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THE RELATION OF CANCER TO OLD AGE. By JAMES EWING, M.D. 461

A SERUM TEST FOR THE DIAGNOSIS OF CANCER BASED ON A NEW THEORY OF ETIOLOGY. By B. GRUSKIN, M.D. 476

THE DIFFERENTIAL DIAGNOSIS OF PRIMARY AND SECONDARY CARCINOMA OF THE BRONCHI. By EDWARD WEISS, M.D. 487

SPONTANEOUS NONRHYTHMIC VARIATIONS IN THE BLOOD-PRESSURE LEVELS AND IN THE "SILENT GAP," A THEORY OF VASOMOTOR ARRHYTHMIA. By LOUIS H. SIGLER, M.D. 494

ACUTE MASSIVE (NONSURGICAL, NONTRAUMATIC) PULMONARY ATELECTASIS. REPORT OF TWO CASES. By HENRY K. MOHLER, M.D. 507

THE VOLUME AND HEMOGLOBIN CONTENT OF THE RED BLOOD CORPUSCLE. SIMPLE METHOD OF CALCULATION, NORMAL FINDINGS, AND VALUE OF SUCH CALCULATIONS IN THE ANEMIAS. By MAXWELL M. WINTROBE, M.D. 513

BLOOD SEDIMENTATION TEST COMBINED WITH A SERUM REACTION IN THE DIAGNOSIS AND PROGNOSIS OF TUBERCULOSIS. A PRELIMINARY STUDY OF ONE HUNDRED AND FORTY-SEVEN CASES. By EUGENE M. SCHLOSS, M.D., and PHILIP R. MILLER, M.D. 523

THE ARTIFICIAL PRODUCTION OF PUNCTATE BASOPHILIA AND RETICULATION IN ERYTHROCYTES. By W. E. COOKE, M.D., F.R.C.P.E., M.R.C.P. 537

POLIOMYELITIS. ITS PRE-PARALYTIC PERIOD WITH RESULTS OF SERUM THERAPY. By WARDNER O. AYER, M.D. 540

CERTAIN NERVOUS COMPLICATIONS FOLLOWING THE USE OF THERAPEUTIC AND PROPHYLACTIC SERA. By FOSTER KENNEDY, M.D., F.R.S. (EDIN.) 555

SEX, AGE AND SEASONAL DISTRIBUTION OF TETANY IN THE ORPHANAGES IN PEKING. By SHIH-HAO LIU, M.D., and FU-TANG CHU, M.D. 559

CARBON DIOXID IN THE TREATMENT OF HYPOSTATIC PULMONARY CONGESTION. A PRELIMINARY REPORT. By ROBERT E. BURNS, M.D., and WILLIAM S. MIDDLETON, M.D. 564

THE TOXIC PSYCHOSES: AN ANALYSIS OF ONE HUNDRED CASES. By F. C. HILL, M.D., and GEORGE WILSON, M.D. 569

INDEX TO PHYSICIANS' SUPPLIES . . . . . ADV. PAGE 42

Contents continued on page x

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

APRIL, 1929

ORIGINAL ARTICLES.

THE RELATION OF CANCER TO OLD AGE.*

By James Ewing, M.D.,

PATHOLOGIST TO MEMORIAL HOSPITAL, NEW YORK.

That cancer† is a disease of old age is one of the cherished tenets of clinical medicine. Contrasted with the comparative rarity of the disease in youth, its common occurrence after middle life and great frequency in advanced ages, have led many to conclude that cancer may almost be considered a function of senescence and a somewhat natural outcome of senile changes in the organs. Yet, a review of the literature fails to reveal any very critical investigation of the basis of this common tenet, most observers being content to record statistics showing the age periods when cancer is most frequent. When, however, one begins to consider the real significance of the supposed relation of old age to cancer, one immediately encounters numerous problems of considerable complexity. What is meant by "old age?" Is the incidence of cancer in old subjects an accident, or is it the result of factors essentially connected with the aging process? At what period of life may one consider that old age is established and is the period always the same in different races and individuals? What is meant by "cancer?" Is it always essentially the same disease with a uniform etiology, or does this term cover a multitude of diseases with varying causation? How shall we dispose of the numerous malignant tumors of infancy and youth? Are there any tumors peculiar to advanced ages, and are there any peculiarities of ordinary tumors which may be attributed solely to the age factor? These are some of the inquiries which must be

* Contributed to Old Age Fortnight of the New York Academy of Medicine, October 1928.

† The term cancer is here used to include both sarcoma and carcinoma.

answered before one can determine whether there is any real clinical significance in the relation of cancer to the age factor.

It is first necessary to determine the age incidence of the different forms of cancer. For this purpose there are available adequate statistical studies of considerable scope and reliability.

In 1905, Lazarus-Barlow made an elaborate study of the age incidence of cancer in 4659 female and 2073 male patients dying from cancer in the Middlesex Hospital, London. His table gives a valuable index showing the age incidence of the various forms of cancer in both sexes, as patients apply at a general hospital. These figures have not been considered in relation to the total population living at the different periods. They reflect the general clinical experience that cancer occurs most frequently between fifty and sixty years. (Table I.)

TABLE I.—TABLE SHOWING THE VARIOUS SITES OF PRIMARY CANCER ARRANGED IN ORDER OF THE COMPUTED AGES AT WHICH THEY ARE LIABLE TO OCCUR.

(Compiled from 2073 Male and 4659 Female Cases in the Records of the Middlesex Hospital.)

Age.	Males.				Females.			
	Site of growth.	I.	II.	III.	Site of growth.	I.	II.	III.
45 to 49	Breast	52.263	42	**46.8**	Uterus	46.707	47	**46.8**
	Scrotum	47.417	47	**47.2**	Vagina	49.725	45	**47.3**
					Breast	51.434	47	49.2
					Tongue	52.171	47	49.5
50 to 54	Penis	52.290	52	**52.1**				
	Stomach	52.339	52	**52.2**	Esophagus	49.700	52	50.8
	Larynx	55.954	50	**52.9**	Rectum	51.437	52	51.7
	Tongue	54.587	52	**53.4**	Larynx	53.600	52	52.8
	Colon	55.372	52	53.7	Pancreas	54.414	52	53.2
55 to 59	Bladder A	59.920	52	55.8	Colon	53.276	57	55.1
	Esophagus	55.666	57	56.3	Vulva	55.682	57	56.3
	Liver	53.836	62	57.8	Stomach	52.042	62	56.8
	Rectum	54.086	62	57.9	Mouth (excluding lip and tongue)	56.727	57	56.9
	Mouth (excluding lip and tongue)	55.314	62	58.5	Bladder	59.478	57	58.2
	Pancreas	57.200	60	58.6	Liver	55.414	62	58.6
					Skin	55.946	62	58.9
					Lip	60.714	52	59.7
Above 60	Rodent cancer	58.261	62	60.1				
	Lip	58.668	62	60.3				
	Skin	60.233	62	61.1	Rodent cancer	55.347	67	63.1
	Anus	61.800	62	61.9	Anus	66.857	62	64.4
	Bladder B	59.920	67	63.4				
	Prostate	67.400	72	69.7				

Column I, mean age of all cases. Column II, mean age of quinquennial period in which maximum number of cases occurred. Column III, average I and II.

It is important that in this series about 80 per cent of the cases were cancers of the uterus and breast. In males, cancer of the breast and scrotum occurred early; cancer of the liver, rectum, mouth and pancreas occurred very late. In females the order is much the same, but the early occurrence of cancer of uterus, vagina, breast and tongue is noteworthy. In both sexes, cancer of the generative system affords the early cases, cancer of the skin the late cases, and cancer of the alimentary tract gives the intermediate group. A period of twenty-three years separates the acme of early and the late cases.

Many other similar studies have yielded much the same results, so that it must be regarded as fully proven that the greatest number of cancer cases occur at and shortly after middle life, and between the ages of fifty and sixty years. This fact becomes more significant when it is considered in relation to the number of persons living at this decade as compared with other life periods. The U. S. Census Report on Cancer, 1914, shows that in the Registration area there were about 12,000,000 persons living at each decade from ten to thirty years; 9,200,000 between thirty and forty; 7,000,000 between forty and fifty, and only 6,000,000 between fifty and sixty, and thereafter about a 50 per cent decrease in each succeeding decade. So it appears that the greatest number of cancer deaths occur at a time when the total population living at that period is considerably reduced.

The Metropolitan Life Insurance Company has made a very exhaustive and valuable analysis of the cancer deaths among its policyholders, covering the twelve-year period, 1911 to 1922. They found a slight increase and upward trend, especially marked after fifty-five years, while between thirty-five and fifty-five years the trend was downward. The gravity of the cancer situation is thus concentrated on the older ages, not only from the standpoint of maximum incidence, but from that of increasing mortality. Two per cent of all the cancer deaths were of persons under twenty-five years of age, due to the occurrence of sarcomas. The deaths from cancer of the uterus, rectum and anus, were excessively high among colored women. The upward trend of the death rate from cancer of the intestinal tract was more pronounced than for any other group, and was most marked after fifty-five years. Breast cancer caused 13.8 per cent of the deaths among white females, the rate was even higher among colored females, and it was increasing for both races. The trend of the death rate for buccal cancer was downward between 1911 and 1922, except for colored males. An interesting fact was the higher death rate from cancer of the skin among whites, as compared to negroes. The death rate from cancer of the skin gave 4.1 per cent of all cancer deaths among white males, 2.1 per cent for colored males, 1.8 per cent for white females, and 0.9 per cent for colored females.

The great value of this study lies in the separate consideration of different forms of cancer in different races, since the results give a clue to the action of specific factors entering into causation.

The foregoing studies show that the greatest number of cancer cases occur just after middle life; but they do not show whether there is an increasing liability to cancer from the beginning to the end of life, and especially in the advanced age periods. Two important studies refer to this interesting inquiry. In 1905, Bashford published an analysis of 3576 cases collected from the London Hospitals and confirmed by pathologic diagnosis, and considered the age incidence of the cases with the total population living at the various periods. (Table II.)

He found that there is a progressive increase in the liability to nearly all forms of cancer at each age period up to eighty-five years, after which there was a slight, but unimportant decline. The occurrence of a very high proportion of cancers of skin, tongue in males and of breast in females is worthy of note. Only tumors of the brain showed a marked decrease after seventy-five years. This table also shows the well-known fact that the period between five and ten years is marked by a notable incidence of tumors of the brain, kidney and adrenal. The lowest incidence of the disease, as a whole, occurs about the tenth year, after which there is a continuous increase in the total number of cases and in the liability. The same conclusions must be drawn from the U. S. Census Report of 1914. (Table III.)

This table shows a continuous increase in the liability to cancer at all age periods up to eighty-five years, with a slight decrease beyond that period. The increase is remarkably uniform for all forms of cancer except tumors of the brain.

Somewhat divergent results were obtained by Weller, but in a selected material coming to a general hospital. Weller determined the age incidence of 1106 cases of cancer diagnosed in the Ann Arbor Laboratory. There was a steady increase in the number of cases up to the sixtieth year, with a progressive decrease thereafter. Compared with the population living at the different periods, the greatest incidence of cancer was, for females, between fifty-eight and sixty-two years, for males between sixty-eight and seventy-two years, followed by a slow decline up to eighty-two years. The earlier incidence of cancer of the uterus and breast accounted for the discrepancy between the sexes.

At the Mohonk Conference, Dublin presented an important study of the chances of dying of cancer at the different age periods, based upon an analysis of 125,000 cancer deaths among the policyholders of the Metropolitan Life Insurance Company in the years 1910, 1922 and 1924. In 1910, among 100,000 persons living at the age of ten years, there would be 5874 cancer deaths up to the

TABLE II. — ENGLAND AND WALES.

TABLE II.—ENGLAND AND WALES.

Deaths per 1,000,000 Living at Each of the Age Periods Given. Average 1901 to 1904, Illustrating the Different Age Periods at which Cancer of Certain Organs Begins to Increase Rapidly in Frequency.

	Under 5 years.	5 to 10 years.	10 to 15 years.	15 to 20 years.	20 to 25 years.	25 to 35 years.	35 to 45 years.	45 to 55 years.	55 to 65 years.	65 to 75 years.	75 to 85 years.	85 and upward.
MALES.												
Skin	0.79	0.28	0.46	0.61	1.00	2.37	10.53	36.34	103.39	278.49	734.23	1650.20
Stomach	...	...	...	0.15	2.33	15.08	89.69	325.62	875.64	1530.94	1490.714	736.45
Rectum	0.13	...	0.46	0.91	4.83	10.94	35.90	142.54	393.57	718.54	826.19	668.26
Tongue	...	...	...	0.15	...	1.58	21.82	114.10	224.59	278.73	305.56	1772.94
Brain	3.30	3.38	2.49	2.90	3.33	6.31	10.66	16.50	20.25	13.34	2.97	
Shoulder	0.26	0.14	0.29	0.61	0.83	0.89	1.01	2.11	4.05	8.72	14.83	13.64
Kidney and adrenal	7.93	1.69	0.73	0.46	1.17	1.77	5.71	16.68	33.47	45.65	54.88	13.64
FEMALES.												
Skin	0.53	0.14	0.15	0.15	0.30	1.06	4.39	15.29	32.65	97.87	267.48	553.62
Stomach	0.13	...	0.15	0.15	1.04	12.38	79.27	278.78	678.29	1195.33	1255.77	834.43
Rectum	...	...	...	1.49	2.23	11.05	36.31	122.80	271.13	441.44	552.15	312.91
Uterus	0.26	...	...	0.45	3.30	61.99	337.25	746.34	967.16	1012.29	910.94	730.13
Breast	...	...	0.15	0.15	0.74	20.16	168.86	460.28	699.11	966.42	1407.23	3013.88
Tongue	0.13	...	...	...	0.15	2.21	3.68	7.64	17.98	42.18	49.41	24.07
Brain	1.32	2.10	1.76	1.64	2.97	4.33	9.85	11.55	13.49	10.65	6.45	
Shoulder	...	0.28	0.29	0.45	0.30	0.71	0.95	1.30	4.02	4.91	7.52	8.02
Kidney and adrenal	8.16	1.54	0.59	0.60	0.59	1.33	5.70	16.92	28.39	43.41	54.79	24.07

TABLE III.—PROPORTION OF CANCER DEATHS TO TOTAL POPULATION LIVING AT EACH AGE PERIOD, U. S. CENSUS REPORT, 1914.

Death Rate per 100,000 Population by Sex and in the Age Group Specified.

	Under 25 years.	25 to 34 years.	35 to 39 years.	40 to 44 years.	45 to 49 years.	50 to 54 years.	55 to 59 years.	60 to 64 years.	65 to 69 years.	70 to 74 years.	75 to 79 years.	80 to 84 years.	85 years and over.
Male	2.8	8.7	21.5	43.0	78.9	140.9	237.7	339.8	467.0	627.4	684.2	826.4	824.3
Female	2.7	19.6	64.7	118.7	184.4	266.5	381.1	449.4	566.6	717.1	845.5	946.2	916.7
Total	5.5	28.3	86.2	161.7	263.3	407.4	618.8	789.2	1033.6	1344.5	1529.7	1772.6	1741.0

end of life, but in 1924, the calculated deaths had increased to 8652, (47.3 per cent), owing to the reduction of deaths from other causes. Dublin comments on the alarming significance of this conclusion, since the reduction of deaths from other causes is bound to continue and more and more people will reach the cancer age and eventually die of this disease. He thinks that the attitude of the medical and public health professions toward cancer should be revised and greatly increased efforts made to meet the problem.

Very similar conclusions were reached by Schereschewsky from a study of the U. S. Census Reports.

It is necessary to point out a possible misinterpretation of these statistical studies. They do not show that there has been any increased tendency toward cancer in any individuals at any age. They merely show that people are living longer, so that the lapse of time permits the expression of whatever tendency to cancer they may possess. The liability of exposure to exciting factors of some cancers, as of skin and lung, may have increased in the past twenty-five years, but these studies do not prove this to be a fact.

A comparison between the white and colored races appears in the study of Pearl and Bacon. They analyzed 6670 autopsied subjects at the Johns Hopkins Hospital, among which there were 816 cases of malignant tumors, or 12.2 per cent. This percentage is somewhat higher than that of the general population. Their main conclusions were that cancer occurs much more frequently in whites than in negroes, and slightly more often in females than in males. The highest proportion of cancer deaths, compared with total deaths occurred between the ages of fifty-five and sixty-five years, except for females, with whom the mortality from uterine cancer seems to have advanced the main period of deaths about five years. They do not consider the relation of total cancer deaths to total population living in the different age periods, but quote Dublin's observations which show that there is an increasing chance of death from cancer up to the end of life.

Both the above types of statistical studies suffer from some inaccuracies. In the census material, large numbers are involved, but the diagnoses are uncertain, while in the hospital material in which the diagnosis is certain the cases are more or less selected. The fact that the results from both classes of studies are identical seems to assure the general reliability of each.

Some interesting details regarding the cancers of old age are furnished by the report of Roussy, Le Roux and Vermes of 1000 autopsies occurring in a home for the aged. Among these autopsies there were 77 cases of cancer, 32 in males, 45 in females, 39 clinically recognized, 38 found at autopsy. The distribution was as follows:

TABLE IV.—DISTRIBUTION OF CANCER OF THE AGED.

Decades, years.	No. cases.	Organ.	Cases.	Organ.	Cases.
50 to 59	2	Stomach	27	Lung	2
60 to 69	14	Uterus	8	Gall bladder	2
70 to 79	32	Skin	5	Bladder	2
80 to 89	19	Colon	5	Liver	2
90 to 99	1	Kidney	5	Thyroid	2
	—	Pancreas	5	Breast	1
	68	Rectum	3	Tongue	1
Unknown	9	Esophagus	3	Unknown	4

There was only one sarcoma, type not stated.

The authors emphasize the important part played by infection as the cause of death in these cases. Death was attributed to cancer cachexia in 24 cases, to cancer plus infection in 6, and to intercurrent infection in 47. Probably much the same results would be revealed by a study of cancer deaths at other ages, but they suggest that in old subjects the progress of cancer is somewhat less rapid than at other ages, and that intercurrent infection plays a larger part in the disease in old persons than in younger subjects.

The high incidence of cancer in old age is not limited to human beings, but probably exists in all species of animals.

Old dogs are especially prone to develop such tumors and it is rare to find an old dog over fifteen years of age which does not exhibit one or more benign or malignant tumors. Goodpasture and Wislocki found tumors in all of 15 old dogs which showed signs of senility such as loss of teeth and cataract. In most of the animals several organs contained tumors. The tumors were adenomas of the liver and adrenal in most cases, adenomas of thyroid, papillary adenomas of gall bladder, stomach, ovary, prostate and pancreas, cystic adenoma of thymus, angiomas of spleen, lipomas and fibromas. Mammary cancer is so common in old bitches that such animals cannot safely be used for the experimental production of mammary cancer.

Cohrs found 77 tumor-bearing domesticated animals among 737 autopsies; and of the 77, the tumors were multiple in 26. He noted the greater frequency of tumors in older animals, and especially their multiple character. In the causation of these tumors he laid greatest importance on the congenital abnormalities in structure and on recurrent chronic irritations.

The foregoing studies seem quite adequate to show these main facts: first, that the greatest incidence of cancer occurs shortly after middle life; second, that there is an increasing liability to cancer practically up to the end of life; and third, that the liability to cancer has increased greatly in the last two decades. However, the real medical significance of these facts remains entirely unexplained. One may accept the economic importance of statistical facts presented without admitting that they prove any essential connection of can-

cer with senility. Automobile accidents, multiplication of grandchildren, and accumulation of wealth all belong especially to old persons, but they have nothing to do with the process of senescence. One must inquire into the reasons for the occurrence of cancer in old persons. This inquiry leads at once into many complicated questions.

What is old age? Is it to be accepted merely from the chronologic side, or is it to be considered from the physiologic standpoint? Now, it is at once apparent that the changes of senescence occur at very different periods in different individuals, since some age rapidly, and others slowly. Moreover, the changes of senility are very prone to affect one organ before another. Unless one limits the observations to very advanced periods, as after seventy years, one will include in the category of senility many persons who show very little, and some who show no definite senile degeneration of the organs. I have often been struck at autopsies on subjects dead of epidermoid carcinoma at very advanced age, with the remarkable preservation of the organs. In these cases the disease had resulted from strictly local factors, not connected with age. It is unsound to assume that every person who dies of cancer at the age of seventy-five has contracted the disease because of senility. This is one of the reasons why crude statistical studies must always fail to yield wholly reliable indications in this field.

Another source of error lies in the fact that the date of death from cancer does not always indicate even the approximate period of the inception of the disease. Much less does it indicate the time of initiation of the process which led to cancer. On this account, many authors have concluded that statistics cannot bring us any nearer to a solution of the biologic problem of cancer, nor establish an essential relation of the disease to old age.

Mertens refers to the considerable number of cases of cancer in young subjects. He notes the occurrence of the changes of senility in the organs of young adults, and he records several cases in which the recognition of the disease came many years, even twenty-five, after the beginning of the process. Thus he is unwilling to admit that any essential connection between cancer and old age has been demonstrated. Freund, Lewin and others reach much the same conclusion.

Particularly important in this connection is the principle of action of the cancerigenic agent, at a distance in time. Aniline cancer of the bladder may develop many years after the exposure to the irritant has ceased. One observes cases of cancer of the skin developing many years after the application of hot tar. Cancer of the lip and of the anus are notably frequent in advanced years, but they probably result from the cumulative action of many forms of irritation spread over many years. The effective exciting factors in cancer are thus very often hidden and their effects postponed for

many years, so that the date of appearance of a cancer may not at all indicate the date of origin of the process. It is very difficult or impossible to estimate how frequently the appearance of cancer is thus delayed, but it seems certain that a long evolution of the cancer process occurs in a high proportion of cases. We must, therefore, conclude that many cancers appear in old age, not because they are the result of any element of senescence, but merely because the lapse of time allows the fruition of processes which have their inception at a much earlier period.

What are the factors in senescence which may tend to produce cancer and how often are they actually found to be the main basis of the disease? Among the conditions found in the bodies of old subjects, there are three which are of obvious importance in this inquiry: (1) atrophy of the parenchyma of organs, often attended with deposit of pigment; (2) replacement fibrosis; (3) arteriosclerosis. It seems probable that the controlling element in all these processes lies in changes in the bloodvessels, both large and small. In each organ the changes produced are characteristic. In the skin there is atrophy of the elastic tissue, thinning, dryness, pigmentation and hyperkeratosis. The atrophy of subcutaneous fat produces wrinkles. In the liver there is simple atrophy with pigmentation, and some replacement fibrosis. All glands of internal secretion show cellular atrophy and fibrosis which are, at times, pronounced. The kidneys are reduced in size, indurated, and usually show some cortical areas of atrophy from narrowing of bloodvessels. All mucous membranes tend to show reduction in glandular tissue and lymphoid stroma. The special sense organs suffer atrophy of the specialized cells and fibrosis. The lymphoid tissues are much reduced in bulk and may exhibit complete atrophy. In the bloodvascular system, there is general reduction of muscle and elastic tissue, causing reduced circulation. The bones contain excess of calcium and are brittle, while the cartilages and joint capsules are often calcified, atrophied and inelastic. The red marrow disappears, except in the vertebræ and flat bones. The blood volume is reduced.

From the physiologic side, all these changes tend to produce lowered functional and metabolic activity.

Many authors have urged the prime importance of arteriosclerosis in the origin of cancer, but extremely few have given any data of real value on this subject. Warner studied 206 cases of cancer and found arteriosclerosis in the affected organ in 105 (51 per cent); fibrosis in 127 (57 per cent). This report is a fair index of the association of cancer with arterial disease in the average material, but arteriosclerosis is probably much more frequent in old subjects. There are a few characteristic forms of cancer in old subjects, which are referable to arteriosclerosis, but this lesion is absent in a large proportion of cases at all ages. Even when present it may not be an important factor in the genesis of cancer.

It is at once evident that none of these conditions, briefly enumerated, give any direct clue to the origin of cancers, and it becomes necessary to analyze the conditions in far greater detail in order to establish a connection between old age and cancer. However, one general factor common to all the above states may be recognized as of importance. Thiersch conceived that in the tissue atrophy of old age the connective tissues offer less resistance to the better surviving epithelial tissue, so that abnormal epithelial proliferation occurs more readily. This theory assumes that there is more atrophy of connective than of epithelial tissue, and it fails to account for the atypical character of the proliferation, but it has generally been accorded considerable importance.

To trace the changes of old age into cancer is a very difficult problem since it involves a knowledge of the very beginnings of cancer in the different organs, and these beginnings have seldom been observed. Here the inquiry must be quite detailed and specific and directed to each particular cancer in each organ. A comprehensive study of this subject cannot be attempted in the scope of this communication, but a brief effort may be made to trace some of the cancers of old age to the conditions essentially belonging to this period of life.

Cancer of the Skin. Pigmented epidermoid cancer of the skin, or malignant lentigo, is a well-known tumor of the skin which is clearly connected with the aging process. It begins in one or more small pigmented spots, which gradually enlarge, coalesce, become heavily pigmented, and after many years begin to show infiltrative growth with marked malignancy. It is not a true melanoma, but an epidermoid carcinoma. It is often associated with general xeroderma pigmentosa. The sclerosis of the derma, and the accumulation of pigment belong to the process of senescence. How they combine to produce cancer is unknown. The process extends over many years, so that the inception cannot be ascribed to old age alone, and there is the further difficulty that very similar pigmented atrophy of the skin resulting in carcinoma occurs in young subjects. Indeed one must admit that the essential process, which consists in a disturbance in the pigment forming function, probably hereditary, has no essential connection with senescence, but merely requires the lapse of time to express its results.

Senile angioma must be regarded as essentially a disease of old age, at least in respect to frequency and number of lesions. It is said that at least 75 per cent of all subjects over sixty years of age present these tumors, sometimes in very large numbers. They are varicosities in the small bloodvessels of the skin and may be referred to gradual atrophy of the elastic tissue.

Rodent Ulcer. Although common at earlier ages, this disease finds its greatest incidence in advanced years, especially after eighty-five years. The explanation of this fact involves some difficult questions.

Most rodent ulcers are derived from hair follicles, others from congenital epidermal rests. Long-continued chronic irritation doubtless plays a rôle, but it seems necessary to assume that the senile atrophy of the skin does not equally affect all hair follicles and that some chronically irritated follicles retain powers of growth which enable them to proliferate and acquire malignant properties. Thiersch's theory of diminished resistance of connective tissues has been commonly employed in this connection. Indeed one may here point out an important principle which governs senile atrophy in all organs, namely, that during the atrophic process surviving epithelial tissues may not only escape atrophy, but may exhibit increased powers of growth which tends to assume malignant properties. This principle is also exhibited in the sudden and excessive growth of single hairs which often appear on the skins of aged persons. The complete explanation of the phenomenon, as usual, escapes our detection, but the observation must be regarded as one of the most important data on which tumor growth may be referred to the aging process.

Mammary Cancer. After the skin, the female breast, in Bashford's tables, shows the most notably increased incidence after sixty-five years, and especially after seventy-five years. This fact is not generally recognized. I have been unable to determine that mammary cancer in the aged presents any characteristic features. Generally, the cancers of the aged run a slow course, but in the breast there are not a few cases in which the disease is unusually rapid and the structure highly atypical and malignant. A rapidly growing hemorrhagic carcinoma of the nipple, observed at the Memorial Hospital, illustrates this group. It does not appear clearly that scirrhous cancer is more common in the aged than at earlier periods. While the precancerous changes in these cases doubtless occupy many years, the actual outbreak of the disease must be referred to the conditions belonging to the senile period. The rapid course of certain cases must be referred to inherent properties of the tumor cells, and not to lack of defensive mechanism in the atrophic sclerosed tissues, since the latter factors are present in the scirrhous cases.

Gastric Cancer. Cancer of the stomach shows its highest relative incidence between sixty-five and seventy-five years (Bashford), and it remains high after eighty-five years. I know of no data which may explain this fact, nor of any peculiar features of gastric cancer in the very aged. Horsley reports 5 cases of gastric carcinoma without peculiar features in subjects over seventy years of age, and comments on the favorable results of operation upon them. After sixty-five years, I have observed nearly all forms of gastric cancer, except the bulky adenocarcinoma. These include early adenocarcinoma of the pylorus, diffuse fibrocarcinoma of the pylorus, diffuse sclerosing carcinoma, linitis plastica, and probably one very remarkable case of ulcero-carcinoma in a female aged seventy-three years, of thirteen years' duration. However, linitis

plastica occurs at earlier ages, and the slow course of fibrocarcinoma must be referred more to the intrinsic properties of the cells than to any factor residing in senility. Increasing glandular atrophy, muscular atony, arteriosclerosis, imperfect mastication, mouth infections, peritoneal bands, and intestinal stasis, may all play a part in the eventual outbreak of gastric cancer in the aged. None of these factors are peculiar to old age, but the lapse of time may permit them to become effective.

Rectal and Sigmoidal Cancer. Rectal and sigmoidal cancer also shows its highest incidence after sixty-five years, and it seems safe to refer this fact to long-continued rectal irritation from fecal stasis, anal disease, prostatic enlargement, and other pelvic obstructions.

Cancer of the Lip and Tongue. Cancer of the lip and tongue in males increases in frequency rapidly after sixty-five years, and very rapidly after eighty-five years. It is not difficult to find the explanation in the cumulative effects of the well-known forms of chronic irritation which are responsible for these lesions at earlier periods.

That cancer of the entire alimentary tract becomes so very frequent in aged subjects may well be emphasized. Whether the chronic irritations or the acquired predisposition of the tissues are the more important factors may be debatable, but the facts seem to call for special cautions and hygienic efforts directed to the prevention of these forms of cancer. In the aged their prognosis is extremely unfavorable.

Uterine Cancer. While the greatest number of deaths from this disease falls in the fifth decade, and at a comparatively early age, the highest incidence in proportion to the number of women living is not reached until after sixty-five years, and the proportion remains high to the end of life. Corpus carcinoma especially belongs to the later periods. The typical corpus carcinoma of elderly women and spinsters occurs in a small atrophic uterus and usually involves the entire endometrium. It arises on the basis of atrophic endometritis, in which isolated glands escape atrophy and proliferate slowly. These cases illustrate the principle already stated of the malignant proliferation of isolated cell groups in an atrophying organ. Although exactly similar conditions arise in earlier periods, when precocious atrophy occurs, the disease must be assigned essentially to senescence.

Ovarian Tumors. These are frequent in early ages, and are well distributed over other periods, but there is a notable group of very malignant, rapidly fatal cases occurring in old subjects. I have observed two very anaplastic adenocarcinomas in subjects over eighty years. Isbruch and Werdt both report cases of peculiar granulosa-cell tumors of the ovary, and state that they occur in older women, and are associated with endometrial hypertrophy. However, 3 of Werdt's 6 cases occurred in young subjects.

These very late cases of very anaplastic carcinoma of the ovary are highly interesting, since they occur in atrophic organs forty and

fifty years after functional activity has virtually ceased. They reveal the cancer cell in a sinister light. It may be assumed that in the old atrophic ovary, growth restraints are almost wholly lacking, but the enormous powers of growth of these long slumbering cells are one of the marvels of the tumor world.

Cancer of the Liver. Since the majority of tumors of liver and gall bladder are sequels of long-standing cirrhosis, or cholelithiasis, it is not surprising that the greatest incidence of these tumors occurs at a late period—sixty-two years. (Lazarus-Barlow.) Yet, only two forms of liver cancer appear to be characteristic of old age. One of these is the cancerous cirrhosis, in which an old cirrhotic process terminates slowly in a general cancerous degeneration of the incarcerated liver lobules.

Another form, even more characteristic, is the solitary malignant hepatoma, which while generally occurring in middle life, may appear in elderly subjects without any previous cirrhosis, or premonitory symptom, and run a very rapid course. In one case I found, as the sole symptom, a single fatal hemorrhage into the peritoneum.

Cancer of the Gall Bladder and Bile Ducts. Cancer of the gall bladder and bile ducts, producing a very large liver with jaundice, has a late average incidence, and was long ago classed by Frerich with the essential cancers of old age. The average age, in Futterer's large series was fifty-seven years.

Pancreatic Cancer. The two main forms of pancreatic cancer, one arising from the ducts, the other from the parenchyma, generally follow chronic inflammation of the pancreas, so that the age of incidence of this disease is late. Lazarus-Barlow gave the average age at sixty years. Bard and Pic report several cases after seventy years, and point out the cardinal symptoms; distention of the gall bladder, jaundice, absence of hepatic enlargement, and rapid cachexia.

Cancer of the stomach, liver, gall bladder and pancreas, being inaccessible lesions, probably accounts for the death of many old persons in whom no accurate diagnosis is recorded.

Prostatic Cancer. Cancer of the prostate gave the highest average age incidence in the report of Lazarus-Barlow (seventy-two years). The explanation lies in the fact that this disease usually arises on the basis of chronic prostatitis, which is seldom well established before the sixtieth year. It, therefore, deserves recognition as one of the prime cancers of old men.

Renal Tumors. The various renal tumors are well distributed over all ages, from infancy to middle life, but there is one form of renal cancer which belongs exclusively to old age. This is the multiple adenocarcinoma arising in old arteriosclerotic kidneys. It is of little clinical interest because of its rarity. That many of the ordinary renal and adrenal carcinomas may be expected in old age, is shown by Bashford's reports in which the highest proportional

incidence came between seventy-five and eighty-five years, following a marked increase after fifty-five years.

Bladder Tumors. Although many carcinomas of the bladder occur in old persons, this disease shows no definite relation to old age. In the male, Lazarus-Barlow found two groups, one occurring at fifty-two years, and the other at sixty-seven, but neither of the groups was numerous, and no difference in the etiologic factors was mentioned.

Tumors of the Brain. Tumors of the brain are generally regarded as diseases of early and adult life, but Bashford's tables show a steady increase in proportional incidence up to sixty-five years. Age, therefore, enjoys no immunity to the outbreak of these neoplasms. In the report of Bailey and Cushing, it appears that the spongioblastoma (gliosarcoma), was the only tumor occurring with any great frequency in elderly subjects. This tumor was most frequent in the fifth decade, while the oldest subject was sixty-nine years of age. The etiology of these tumors shows little connection with factors of old age.

Sarcoma. The great immunity of old age to sarcoma finds its main explanation in the reduced activity of the connective tissues, and the early maturation of the bony skeleton. Rarely one observes late myosarcomas of the uterus and gastrointestinal tract and a few neurosarcomas. In the field of bone sarcoma, it is worthy of note that the only osteosarcomas reported in the Registry of Bone Sarcoma, in subjects over fifty years of age, developed on the basis of osteitis fibrosa. In the literature there are a few reports of multiple giant-cell tumors in old persons, usually in connection with osteitis fibrosa.

Summary. The attempt to summarize the conclusions to be drawn from the foregoing data requires the admission that the material is very miscellaneous, fragmentary and inconclusive. The statistical studies prove that the chance of dying of cancer increases up to the end of life, and that this chance is increasing, mainly because people are living longer, possibly also because the exposure to cancerigenic agents and habits is greater. These facts alone are of little clinical or pathologic importance, since they do not prove that all or any great number of these cancers result from the processes of senescence. The mere lapse of time accounts for many and may possibly account for the majority of the cancers of the aged.

I have been unable to find any report of a study of a large number of cases of cancer in old subjects, with the object of determining to what extent the disease was the result of senescence. Such an undertaking would be very difficult and laborious, so much so, that no one seems to have been willing to attempt it. The various textbooks on diseases of old age contain very meager reference to the subject. Only Schwalbe attempts a systematic enumeration of the tumors of old age, but without critical analysis. Yet, a few facts of

medical importance seem to stand out prominently. Senile atrophy of tissues and organs, replacement, fibrosis and arteriosclerosis create local conditions which favor the development of some cancers which may be properly attributed to old age. Some of these true cancers of the aged exhibit peculiar clinical and pathologic features, and several tumors of this type have been enumerated in the previous discussion in this paper. They are, on the whole, not numerous.

During the senile atrophy of tissues and organs, it seems to be a principle of importance that isolated cell groups, gland acini, lobules, and probably tissue rests, escape atrophy and find conditions of growth more favorable. The data support Thiersch's theory of disturbed balance between epithelium and connective tissue.

In this crude sense, cancer may be considered a function of senescence. But, if all other causes of death were eliminated, pneumonia would become the main cause of death of old persons, and in the same sense become a function of senescence.

The main factor which accounts for the high incidence of cancer in the aged is the lapse of time, which permits the natural termination in cancer, of processes which have their inception in adult life, or in youth, in infancy, or even *in utero*. This principle applies to nearly all the tumors arising from tissue abnormalities, and to a great many of those resulting from chronic irritation. That the great majority of tumors of old age may be thus explained, cannot be asserted without much more evidence than is now available, but appears highly probable.

Arteriosclerosis probably plays an important rôle in the development of many cancers in the aged, but it is by no means a constant factor, and its exact significance has never been determined.

If precocious atrophy and arteriosclerosis of single organs are regarded as a phase of senescence, then a strict chronologic classification of cases is unsound, and many cancers occurring in adult and middle life belong in the group of cancers of old age.

Probably the majority of cancers occurring at advanced age periods show exactly the same etiologic factors and clinical course as those occurring in adult and middle life, and their separation as a specific group is unwarranted.

For the same reasons, cancer in the aged must be regarded as always pathologic and not as an essential phase of the process of senescence. Senility merely acts in preparing the soil and rendering the tissue more susceptible to the action of the usual exciting factors, the presence of which is almost as essential as in earlier periods of life.

In general, the cancers of old age pursue a relatively slow course, depending on the reduced metabolism of this age period, but there are many cases which exhibit an unusually rapid growth. These latter probably arise mainly from tissue rests, which have long remained quiescent, but which, when once excited to growth, find conditions especially favorable for unrestrained proliferation.

In the clinical course of cancers in the aged, secondary infection plays a very prominent part and often masks the true nature of the disease. Hence the proportion of unrecognized cancers is higher in the aged than at other periods. Owing to the very high incidence of cancer in the aged, the suspicion of this disease should be kept prominently in mind by diagnosticians.

For the same reasons, special precautions against the outbreak of cancer may well be employed in the very aged.

The detailed study of the action of factors essential to senescence in the origin of cancer in the aged is at present quite inadequate to determine the real influence of old age on the incidence of cancer. Until such studies are available, most of our conclusions in this field must be subject to many limitations.

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A SERUM TEST FOR THE DIAGNOSIS OF CANCER BASED ON A NEW THEORY OF ETIOLOGY.

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Numerous serologic tests for the diagnosis of cancer have been proposed. Although some of these have gained a certain popularity, most of the tests which have been described have failed to survive critical repetition and no serodiagnostic test is today generally regarded as reliable and specific. It is the purpose of this paper to propose a test for the diagnosis of malignant disease based upon principles which differ fundamentally from any of the known tests which have been proposed and to describe the results obtained which are believed to substantiate the proposed theory. Diagnostic tests

for cancer based upon the principles of immunity factors were first attempted by means of complement fixation. These were soon followed by others based upon chemical precipitation and still later by flocculation tests.

In a thorough historic review of the subject, Fry[1] points out that the complement-fixation test which has been extensively used to discover antibodies in the serum was first advocated by Sampietro and Tesa[2] in 1908. Subsequent observers, however, failed to substantiate the results claimed for this test. Other reactions such as the precipitin test used by Engel in 1904, the anaphylactic test studied by Pfeiffer and Finstern[3] and the antitryptic reaction described by Marcus[4] have given variable results. The fallacies of the ferment reaction of Abderhalden were pointed out by Leitch[5] in 1914. A chemical precipitation reaction was described by Kahn and a similar one by Botelho.[7] The latter has been shown by Fry[8] to be of little diagnostic value. The flocculation method was first used by Weil and Braun[9] and followed by a test based on the same principle by Roffo.[10]

Lavedan,[11] using Botelho's reaction on an extensive series of well-controlled cases, concludes that the test is not specific for cancer, that it is not a reaction of cachexia, being often positive in patients with localized lesions and negative in cases of advanced cancer. The exactness of the results depend upon the location of the lesion. In deep-seated cancer (breast, uterus, digestive tract) the percentage of exact results is high and the test has a real diagnostic value. An analysis of the Botelho serum reaction by Baty and Greene[12] of the Huntington Memorial Hospital, also led to the conclusion that the reaction is of no value in the diagnosis of cancer. A flocculation test described by Brossa, Bozzolo and Lombardi[13] gave clearly positive results in growths of the gastrointestinal tract. Noncancerous patients gave positive results in advanced cases of tuberculosis and lues, otherwise, controls were negative. Occasional negative results occurred in lesions of the skin.

In a series of 500 cases of malignant and non-malignant disease, Fry reports 75 per cent correct results. Out of 239 cases of malignant disease, 170 gave positive results (71 per cent) and out of 261 controls, 204 gave negative results (78 per cent). Healthy individuals gave uniformly negative results. Non-malignant tumors usually gave a negative reaction. Positive flocculation occasionally occurred in acute febrile conditions such as tuberculosis and sepsis. The antigen employed was obtained from carcinoma of the breast. A special study of the Thomas-Binetti reaction by Mondain, Douris and Beck[14, 15] led to the conclusion that the results have been obtained because of the fact that the neoplastic extract was not aseptic and they attributed the discoloration of the methylene blue to microbic action. They conclude that cancer serum has not the power to reduce methylene blue.

Theoretical Considerations. As a working hypothesis, it may be assumed that in the ordinary course of normal cell growth, each type of cell produces a lysin against the other type of cell. That is to say, connective-tissue cells normally have the property of generating certain lysins which are antagonistic to excessive growth of epithelial cells, so that although an inciting factor such as chronic irritation may be present, carcinoma does not develop. If, on the other hand, the connective tissue fails to produce such lytic agent, a carcinoma results when the proper extrinsic factors are present. The opposite cycle follows in the production of sarcoma, that is, a deficiency or lack of lytic agent normally produced by epithelial tissue results in the presence of proper extrinsic factors in the production of sarcoma. In other words, the maintenance of an equilibrium between the connective and epithelial tissues is considered as dependent upon the presence of antagonistic lytic agents. The hypothesis of Waldeyer and Thiersch of an equilibrium between the connective tissue and epithelial elements and the tissue tension hypothesis of Ribbert, are in direct accord with this theory. The ability of normal serum and the failure of cancer serum to autolyze cancer cells *in vitro* has been demonstrated (Freund and Kaminer[16]) and points to the presence of a lytic substance in normal blood serum.

This theory is also in accord with the general nature of opposing physiologic forces found in normal biologic activities, where two counteracting principles tend to maintain an equilibrium in normal cell growth, that is, the maintenance of the endocrine balance, the vascular functions of dilatation and constriction and the thermogenetic and thermotactic apparatus.

Based on this conception of the possible cause of malignant disease, it was believed that a lytic agent might be produced by the inoculation of animals with purely embryonic epithelial cells in the case of carcinoma, and connective-tissue cells in the case of sarcoma. In this way, amboceptors would be developed in such treated animals and their sera might have the property when injected into a patient suffering from malignant disease to destroy, in case of carcinoma, embryonic epithelial cells, and in the case of sarcoma connective-tissue cells, based upon the accepted serologic principles of the production of lytic agents.

The second consideration was to demonstrate the correctness of the relationship between malignant new growth and the lytic agent produced by immunizing animals. Experiments were performed to prove the existence of such amboceptors on the basis of the production of precipitins, recognizing that if precipitins were formed between the amboceptor and the serum of a cancer patient, a homologous relationship would be established and it would be demonstrated that no difference exists between embryonic cells of one species of animal and another. In order to determine whether the

precipitin reaction is due purely to the immunizing properties of the embryonic cells, control animals were inoculated with pancreatic tissue obtained from mature animals and it was found that the sera of these animals failed to produce precipitin when brought in contact with the serum of cancer patients. According to J. Ewing, this may be due to the presence in embryonic tissue of specific growth-stimulating substances. Having demonstrated the specificity of the amboceptor produced by immunizing animals with embryonic cells, it was logical to attempt to utilize this immunologic principle as a diagnostic test.

It is important to point out that the principle upon which, the present test is based, differs fundamentally from that of any other test which has been presented in the following ways: (1) Because the test is purely biological in character, and (2) because the amboceptor is produced by means of purely embryonic cells. It should be noted that most of the serodiagnostic tests in which tissue cells have been used have been performed with an antigen composed of both epithelial and connective-tissue cells. Fry, for instance, used breast cancer as an antigen, but adds that cellular carcinoma is preferable to scirrhous cancer. When the theory upon which this test is based is considered, it is readily seen that the presence of adult connective tissue detracts from the specificity of the antigen and it is suggested that this factor may be responsible for the better results obtained with the more cellular growths. It is believed that the complement-fixation test for cancer could be rendered specific if pure embryonic cells such as are employed in our test were used in the preparation of the antigen. Attempts to utilize this principle in a complement-fixation test are under way.

Methods. Preparation of Amboceptor Preliminary Steps. It is essential that in the preparation of the amboceptor both for carcinoma and sarcoma, all glassware and other utensils used be chemically clean, sterile and of a neutral reaction. The serum of the animals is obtained according to the usual method in test tubes of large caliber and allowed to coagulate at room temperature. It is then placed in the incubator for a few hours and then placed in the ice chest to obtain separation of the serum without hemolysis. The serum is then pipetted off into sterile centrifuge tubes, and is then centrifuged to throw down any blood cells which may have remained, so that the serum may be rendered free of substances like chyle, blood cells, and so forth.

Preparation of the Amboceptor for Carcinoma. Mammalian embryos are used (calves, sheep, pigs). They must not be in a later stage than the second month of pregnancy. This is readily recognized by their relative smallness, and by the smoothness of the skin (for instance, there is no formation of hair). In securing these embryos, the abdomen must be opened under sterile conditions. The pancreas and submaxillary glands are dissected out,

and placed in a sterile dish. A hypotonic salt solution is poured over these, and if possible, allowed to freeze, the object being to permit an easier removal of the fibrous capsule. The capsule and the ducts, and so forth, are then removed by careful manipulation with small tissue forceps. The epithelial tissue is picked out. It is placed in a mortar in which sterile copper gauze is inserted (to facilitate the maceration) and macerated. Salt solution is added and thoroughly mixed and rubbed up with the macerated tissue until the fluid becomes milky or opalescent in appearance.

The next step is to inoculate healthy male rabbits intraperitoneally or intravenously as follows: (The method used by the author was the intraperitoneal one.) The inoculations are made three days apart. The first injection was 3 cc.; second injection, 5 cc.; third injection, 7 cc.; fourth injection, 10 cc. and fifth injection, 15 cc. The animal is sacrificed three days after the last injection and serum obtained. The amboceptor is now tested with known positive carcinomatous serum and with a known negative serum, as per procedure given below. Precipitin formation should take place with the positive serum; and no reaction with the negative serum.

Preparation of the Amboceptor for Sarcoma. Umbilical cords are obtained freshly. The blood is squeezed out; the veins are punctured and the blood washed away. It is then cut up in small pieces and placed in a meat press. The Wharton jelly (which must be clear of blood) is placed in a mortar, together with bone marrow obtained from embryos (calves, pigs, sheep, etc.), This is well macerated and mixed. It is then filtered through gauze to clear away the small particles of bony substance which might be present. To this, one-third its volume of salt solution is added and is well shaken. Rabbits are inoculated with the mixture every three days, starting with 1 cc. and increasing the dose 2 cc. at every inoculation until five inoculations have been given. The animal is then sacrificed two days after the last inoculation. The serum is obtained as per the previous method for carcinoma. Then it is tested with a known positive sarcomatous serum and with a known negative serum as per procedure given below. Precipitation should take place in the positive serum and no precipitation in the negative serum.

Preparation of the Patient's Serum. As in the preparation of the amboceptor, it is essential that all glassware and other utensils used for the test be chemically clean, sterile and neutral. The serum of the patient is then obtained in the usual manner, and this is done in the morning before the patient has had any food. In order to insure a clear serum, it is preferable to use an 18-gauge needle and a wide test tube. The blood is allowed to coagulate at room temperature. The serum is placed in an incubator for about two hours to secure separation without hemolysis.

Technique of Test. Three small test tubes are placed in a rack. In the first tube 0.3 cc., of amboceptor is placed and carefully over-

layered with 0.9 cc. of patient's serum to which complement had been previously added (3 minims per cc.), (if the serum is older than twenty-four hours). This is overlayered with 0.2 cc. of half normal saline. In the second tube is placed 1 cc. of patient's serum, + 0.4 cc. of half normal saline. In the third tube is placed 1 cc. of amboceptor + 0.4 cc. half normal saline. The rack is then placed in the incubator for five hours without being disturbed. It is advisable to perform two similar tests using a known positive and known negative control as in the Wassermann reaction. After five hours the test is read. Each tube is carefully removed from the rack so as not to disturb the point of contact between the different fluids and is placed against a dark background so as to permit an indirect illumination. In a positive reaction, the result is indicated by a fine white ring at the point of contact of the fluids and a turbidity extending downward. A negative reaction is indicated by the absence of a ring or turbidity, the entire fluid remaining clear. Readings should be recorded as strongly or faintly positive depending upon the degrees of turbidity obtained.

Simplified Modification of Test. In an attempt to simplify the test and make it more useful for practical purposes, it seemed plausible to attempt to utilize the embryonic tissues directly in the form of an antigen instead of the amboceptor produced by animal immunization. In this way, the difficulties encountered in the production of the amboceptor would be eliminated. It was found for instance, that very few rabbits were capable of producing a satisfactory amboceptor. A further difficulty was encountered in the turbidity of the serum in some animals. The following technique was employed in the preparation of the antigen.

Antigen for Carcinoma. The embryonic epithelial cells are prepared as described in the above method up to the point of animal inoculation. At this point, the cells suspended in salt solution are centrifuged until the supernatant salt solution is perfectly clear, the salt solution is then discarded and the epithelial cells are placed in a porcelain dish and dried at a temperature of 75° C. to a doughy consistency. During this period, it is essential that the tissue be stirred thoroughly at fifteen-minute intervals in order to permit uniform drying. The tissue is then placed in a glass-stoppered bottle to which is added three times its volume of acetone. The mixture is permitted to stand in the ice chest for twenty-four hours with frequent shaking. The acetone is then poured off and replaced by one and a half volume of fresh acetone for another twenty-four hours. The acetone is again decanted and the tissue is placed in a mortar to which five times its volume of absolute alcohol is added. This is macerated for about fifteen minutes until the alcohol becomes somewhat milky. The mixture is then kept in the ice box for five days during which time it is forcibly shaken at two-hour intervals. The alcohol extract is then decanted and is ready for use.

Antigen for Sarcoma. A mixture of Wharton's jelly and red bone marrow of calf embryo is macerated in a mortar, to which two volumes of salt solution are added. This is placed in a porcelain dish at a temperature of 75° C. until the mixture becomes grayish in color. The salt solution is then decanted and the tissue is placed in three times its volume of acetone for twenty-four hours. The acetone is then decanted and replaced by one and a half volumes of acetone for twenty-four hours. The acetone is again decanted and the tissue is placed in a mortar and macerated with five times its volume of alcohol for fifteen minutes until the alcohol extract assumes a light-brown color. The mixture is then placed in a glass-stoppered bottle in the ice chest for five days, during which time it is shaken at two-hour intervals. The alcohol extract is then ready for use.

Technique of Test. Five to 10 minims (depending upon titration) of antigen is placed in a test tube, to which 30 minims of suspected serum (which has been previously diluted 50 per cent with normal salt solution) is added slowly drop by drop. This is allowed to stand for two minutes. It is then agitated until flocculation takes place. Ten minims of salt solution is added and is allowed to stand for two minutes. It is agitated again and read against a frosted electric light. A positive reaction is indicated by flocculation. A negative reaction produces no flocculation. It is important that the drops be added slowly and at regular intervals. Adding the drops too rapidly might give a negative reaction in positive cases. It is also important to distinguish between air bubbles and true floccula. The former always rise to the surface, whereas the latter settle to the bottom.

If the suspected serum has a very low specific gravity and looks watery it is best not to mix serum with salt solution, but use it in its original state, as adding salt solution is liable to render a positive serum negative.

Titration. A known positive and negative serum are employed in order to determine the least amount of antigen necessary to produce a positive reaction. When this endpoint is reached, the same amount is used on the known negative and should give a negative reaction. It is essential to determine this endpoint accurately and utilize the least amount of antigen necessary to produce a flocculation. If the known positive of this amount is exceeded by even a few minims, a flocculation might take place in the negative serum.

Precautions. The following precautions should be observed in the preparation of the material: It is essential that the capillary pipettes used in the test should be of equal caliber. It is evident that any difference in the caliber of the pipettes would render the test inaccurate. It is also very important that the cells for the antigen and amboceptor be prepared of pure embryonic cells of

the type desired—for example, the capsules and ducts of the pancreas and submaxillary gland must be removed thoroughly so that no remnants of fibrous tissue will be left. In the preparation of the connective-tissue amboceptor as well as the antigen, Wharton's jelly must be free from blood. The antigen must be dried until it assumes a doughy character—not more nor less than that. Special care should be taken to avoid scorching the tissue while drying. It is essential that the drying process be continuous, proceeding to the finish without stopping.

Advantages. The advantages of the modified method over the immunization method are as follows:

1. Elimination of use of animals in the production of amboceptor.
2. Simplicity of test with advantage of flocculation over precipitation method in facility of reading and interpretation.

TABLE I.—RESULTS OF TEST IN KNOWN MALIGNANT TUMORS.

No.	Case.	Location	Pathologic Report.	Serologic Test.
1	T. C.	Rectum	Adenocarcinoma	Positive
2	T. F.	Breast	Schirrous carcinoma	"
3	N.	Cervix	Squamous carcinoma	"
4	P. G.	Breast	Alveolar carcinoma	"
5	C. E.	Rectum	Adenocarcinoma	"
6	E. S.	Antrum	Squamous carcinoma	"
7	E. F.	Face	Basal-cell carcinoma	"
8	K. T.	Esophagus	Squamous carcinoma	"
9	G. V.	Breast	Adenocarcinoma	"
10	T. P.	Lip	Squamous carcinoma	"
11	V. N.	Stomach	Adenocarcinoma	"
12	V. S.	Gall bladder	Adenocarcinoma	"
13	M. H.	Uterus	Adenocarcinoma	"
14	O. N.	Eyelid	Basal-cell carcinoma ?	Negative
15	McP.	Stomach	Adenocarcinoma	Positive
16	A. H.	Mandible	Squamous carcinoma	"
17	A. R.	Intestine	Adenocarcinoma	"
18	C. P.	Nose	Basal-cell carcinoma	"
19	P. S.	Wrist	Squamous-cell carcinoma	"
20	G. W.	Stomach	Adenocarcinoma	"
21	B. C.	Ulna	Osteogenic sarcoma	"
22	B. T.	Thyroid	Spindle-cell sarcoma	"
23	E. K.	Neck	Spindle-cell sarcoma	"
24	C. B.	Esophagus	Squamous carcinoma	"
25	A. F.	Floor mouth	Squamous carcinoma	"
26	B. 3	Tongue	Squamous carcinoma	"
27	H. O. B.	Lip	Squamous carcinoma	"
28	S. M.	Colon	Adenocarcinoma	"
29	A. R.	Cheek	Squamous carcinoma	"
30	J. F.	Femur	Osteogenic sarcoma	"
31	F.	Tongue	Squamous carcinoma	"
32	S. F.	Breast	Alveolar carcinoma	?
33	M. K.	Breast	Adenocarcinoma	Positive
34	K.	Breast	Duct carcinoma	"
35	W.	Breast	Adenocarcinoma	"
36	B. W.	Cervix	Squamous carcinoma	"
37	W.	Cervix	Squamous carcinoma	"
38	S.	Prostate	Adenocarcinoma	"
39	Dr. K.	Cervix	Squamous carcinoma	"
40	M. G.	Rectum	Carcinoma	"

TABLE I.—RESULTS OF TEST IN KNOWN MALIGNANT TUMORS.
Continued.

No.	Case.	Location.	Pathologic report.	Serologic test.
41	R. L.	Rectum	Carcinoma	Positive
42	I. K.	Stomach	Carcinoma (clinical diagnosis)	"
43	M. E.	Cervix	Squamous carcinoma	"
44	S. Mc.	Breast	Adenocarcinoma	"
45	F. M.	Rectum	Adenocarcinoma	"
46	S. S.	Penis	Epithelioma	"
47	M. H.	Esophagus	Squamous carcinoma	"
48	N. N.	Esophagus	Squamous carcinoma	"
49	M. N.	Rectum	Carcinoma	"
50	Dr. B.	Breast	Adenocarcinoma	"
51	M. J.	Penis	Epithelioma	"
52	M. S.	Face	Basal-cell carcinoma	"
53	N. K.	Stomach	Adenocarcinoma	"
54	M. G.	Stomach	Carcinoma	"
55	M. R.	Stomach	Carcinoma	"
56	S.	Prostate	Carcinoma	"
57	A. H.	Esophagus	Squamous carcinoma	"
58	McD.	Stomach	Carcinoma	"
59	M. O.	Stomach	Carcinoma	"
60	Bed 78	Stomach	Carcinoma	"
61	D. J.	Stomach	Carcinoma	"
62	H. J.	Esophagus	Carcinoma	"
63	R. N.	Stomach	Carcinoma	"
64	J. S.	Stomach	Carcinoma	"
65	P. G.	Esophagus	Squamous carcinoma	"
66	N. B.	Stomach	Carcinoma	"
67	G.	Esophagus	Carcinoma	"
68	N. E. L.	Breast	Adenocarcinoma	"
69	B. W.	Uterus	Adenocarcinoma	"
70	W. E.	Stomach	Carcinoma	"
71	M. H.	Lung	Carcinoma	"
72	A. J.	Breast	Adenocarcinoma	"
73	M. H.	Stomach	Carcinoma	"
74	D. M.	Breast	Adenocarcinoma	"
75	G.	Cervix	Squamous carcinoma	"
76	N. W.	Rectum	Carcinoma	"
77	I. S.	Thyroid	Carcinoma	"
78	J. S.	Pancreas	Metastatic carcinoma	"
79	M. B.	Breast	Alveolar carcinoma	"
80	N. S.	Rectum	Carcinoma	"
81	H. M.	Stomach	Carcinoma	"
82	M.	Rectum	Carcinoma	"
83	M. W.	Stomach	Doubtful histologically	"
84	A. K.	Bladder	Carcinoma	"
85	E. J.	Prostate	Carcinoma	"
86	T. G.	Prostate	Carcinoma	"
87	W. B.	Bladder	Carcinoma	"
88	M. R.	Prostate	Carcinoma	"
89	H.	Breast	Scirrhous carcinoma	"
90	R. S.	Liver	Metastatic carcinoma	"
91	N. M.	Rectum	Carcinoma	"
92	S. R.	Uterus	Carcinoma	"
93	H. C.	Stomach	Carcinoma	"
94	S.	Stomach	Carcinoma	"
95	B. B.	Breast	Alveolar carcinoma	"
96	S. B.	Rectum	Carcinoma	"
97	R.	Rectum	Carcinoma	"
98	R. R.	Esophagus	Carcinoma	"
99	W.	Bladder	Papillary carcinoma	"

TABLE I.—RESULTS OF TEST IN KNOWN MALIGNANT TUMORS.
Continued.

No.	Case.	Location.	Pathologic report.	Serologic test.
100	R. W. 4	Breast	Adenocarcinoma	Positive
101	L. P.	Liver	Metastatic carcinoma	"
102	K. 3	Tongue	Carcinoma	"
103	L. 4	Antrum	Carcinoma	"
104	D. 5	Cervix	Carcinoma	"
105	S. S.	Larynx	Squamous carcinoma	"
106	F. J.	Cervix	Carcinoma	"
107	J. S.	Cervix	Carcinoma	"
108	7 W.	Bladder	Carcinoma	"
109	9 M.	Mouth	Carcinoma	"
110	R. W. 4	Rectum	Carcinoma	"
111	H.	Rectum	Adenocarcinoma	"
112	S.	Penis	Epithelioma	"
113	S. H.	Larynx	Carcinoma	Doubtful
114	M. W.	Cervix	Carcinoma	Faintly
115	S. Z.	Cervix	Epithelioma	Faintly positive
116	M. A.	Breast	Carcinoma	Positive
117	M.	Cervix	Carcinoma	Negative
118	H. H.	Rectum	Carcinoma	Positive
119	E.	Breast	Carcinoma	"
120	H.	Tongue	Carcinoma	"
121	P. 17	Rectum	Carcinoma	"
122	G.	Uterus	Adenocarcinoma	"
123	W.	Uterus	Carcinoma	"
124	T.	Uterus	Carcinoma	"
125	W. S.	Lip	Carcinoma (clinically)	Negative
126	C.	Cervix	Carcinoma	Positive
127	D. E.	Rectum	Carcinoma	Faintly positive
128	G.	Cervix	Squamous carcinoma	Positive
129	G.	Rectum	Adenocarcinoma	"
130	R.	Breast	Alveolar carcinoma	"
131	M.	Stomach	Adenocarcinoma	"
132	C.	Stomach	Carcinoma	"
133	M.	Bladder	Infiltrating carcinoma	"
134	G. L.	Gall bladder	Carcinoma	"
135	R.	Stomach	Adenocarcinoma	"
136	S.	Ilium	Osteogenic sarcoma	"
137	F.	Stomach	Adenocarcinoma	"
138	O.	Colon	Gelatinous carcinoma	"

TABLE II.—RESULTS OF TEST IN KNOWN BENIGN TUMORS.

No.	Case.	Location.	Pathologic report.	Serologic test.
139	H. A.	Leg	Neurofibroma	Negative
140	E.	Breast	Papillary cystadenoma	Positive
141	W. F.	Uterus	Myoma	Faintly positive
142	B. F.	Uterus	Myoma	Negative
143	S. G.	Uterus	Myoma	Positive
144	T. B.	Breast	Benign cyst	Negative
145	S. C.	Uterus	Myoma	"
146	C. L.	Uterus	Myoma	"
147	C. C.	Breast	Benign cyst	"
148	M. I.	Uterus	Myoma	"
149	M. C.	Uterus	Myoma	"
150	O.	Bladder	Papilloma	"
151	S.	Back	Lipoma	"

TABLE II.—RESULTS OF TEST IN KNOWN BENIGN TUMORS.
Continued.

No.	Case.	Location.	Pathologic report.	Serologic test.
152	P.	Uterus	Polyp	Negative
153	R.	Uterus	Myoma	"
154	M.	Uterus	Myoma	"
155	J.	Uterus	Myoma	"
156	P.	Uterus	Myoma	"
157	T.	Ovary	Simple cyst	"
158	R.	Uterus	Myoma	"
159	E. D.	Jaw	Epulis	"

TABLE III.—RESULTS OF TEST IN NON-MALIGNANT DISEASE.

Disease.	No. of cases.	Negative.	Positive.
Endometritis	12	12	0
Diabetes	72	70	2
Lues	61	60	1 (Leukoplakia of tongue
Pernicious anemia	3	3	0
Nephritis	27	27	0
Thyroid disease	156	152	4
Tuberculosis	5	5	0
Osteomyelitis	4	3	1 (Faintly pos.)
Mastitis	5	5	0
Amebic dysentery	1	0	1*
Polycythemia	2	2	0

* Serum contained chyle.

TABLE IV.—RESULTS OF TEST IN NORMAL ADULTS.

No. of cases	146
Negative	143
Positive (faintly positive)	3

Summary and Conclusion. 1. The theory has been proposed that normal tissue equilibrium is dependent upon a balance maintained by the opposing action of lytic agents produced respectively by connective tissue and epithelial cells and that neoplasia is the result of a lack of such lytic agents on the part of the tissue invaded.

2. Based upon this theory a diagnostic test for malignant disease has been developed.

3. The principle of this test is based upon the homologous relationship between embryonic cells and the sera of patients suffering from malignant disease.

4. The homologous nature of embryonic cells of different mammalians has been demonstrated by the ability to develop amboceptors and antigens with embryonic cells of different mammals.

5. A new source and technique for obtaining embryonic cells has been developed and described.

6. This test has been employed in a group of cases of malignant and non-malignant disease and results obtained which tend to substantiate the proposed theory and validity of the test.

7. The results obtained are of theoretical interest in substantiating the proposed hypothesis and are believed to be of practical importance in the serodiagnosis of carcinoma and sarcoma.

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THE DIFFERENTIAL DIAGNOSIS OF PRIMARY AND SECONDARY CARCINOMA OF THE BRONCHI.

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In a recent paper on primary carcinoma of the bronchi by McCrae, Funk and Jackson[1] attention was called to the growing importance of this lesion as a clinical entity. In a study of cases collected from the literature and 14 cases personally observed they conclude that carcinoma of the lung originates in the majority of instances from the bronchus and that this form of carcinoma is increasing in frequency. They emphasize the necessity for bronchoscopy in early diagnosis so that proper treatment may be instituted and call attention to the fact that the early symptoms are those of bronchial irritation and the early signs those of bronchial obstruction. In a study of several recent cases I have been particularly impressed by two points of special diagnostic importance brought out in their work. The one is the frequency of secondary abscess formation in the lung peripheral to the new growth (due to the bronchial obstruction). Under such circumstances, the symptoms and signs of pulmonary abscess may so dominate the clinical picture as to

obscure the diagnosis of the underlying lesion, that is, the bronchial carcinoma.

The second point is that metastases from bronchial carcinoma to the nervous system, abdomen or bones may produce striking clinical manifestations and thus obscure the evidence pointing to the original new growth. This was particularly emphasized in an earlier paper by Fried[2] who was more impressed than the above-mentioned authors with the tendency of bronchial carcinoma to extrathoracic metastases. An unusual example of such an occurrence was reported by Thomas, Hirsch and Blaine.[3] They recorded a case in which the clinical symptoms throughout were associated with alterations of the bones due to metastasis from a primary carcinoma of the bronchus which was not found until an examination of the lungs had been completed some time after the postmortem examination.

One additional feature that enters into the question of the diagnosis of bronchial carcinoma and serves as a special basis for this report is the exact reverse of the point just mentioned; in other words, the occurrence of metastases from an extrathoracic new growth to tracheobronchial lymph nodes causing bronchial compression (and in certain instances actually invading bronchial wall) thus producing chest symptoms and signs simulating primary bronchial carcinoma.

The first case to call my attention to this possibility follows:

Case Reports. CASE I.—A. K., aged fifty-one years, a white man, was admitted to the service of Dr. Chevalier Jackson, October 14, 1927. He complained of cough with slight expectoration of mucus, shortness of breath, huskiness of the voice and loss of weight. The family history was negative. The past history was essentially negative.

The present illness began about a year ago with cough and expectoration which gradually increased in amount. For about three months before his admission there was considerable loss of weight, and shortness of breath became troublesome. During the same period, because the Wassermann test was reported positive, 20 intravenous injections had been given.

Physical examination on admission showed a fairly well-nourished patient with slight dyspnea. The fingers were clubbed. The larynx showed congestion of the mucous membrane, and the left side appeared fixed; the left ventricular band was inflamed and enlarged, and overhung the left cord. The neck was negative. The heart was apparently normal in size and no abnormal sounds were heard. Expansion was limited and the percussion note was dull over the lower two-thirds of the right chest. The breath sounds were tubular and distant and many large musical râles were heard. The left lung was clear and resonant throughout and the breath sounds were exaggerated. Physical examination otherwise was negative. The temperature on admission varied between normal and 101°, the pulse rate was 100 and the respirations 30. The expectoration varied from 6 to 14 ounces in the twenty-four hours. On standing it separated into two layers of which the lower was practically clear and consisted of about 75 per cent of the total quantity. Repeated examinations failed to show tubercle bacilli. The blood Wassermann test was negative and urine examinations were practically negative.

FIG. 1.—Case I. Abscess of lung, with fluid level, lower portion of right upper lobe, secondary to bronchial compression caused by metastatic new growth.

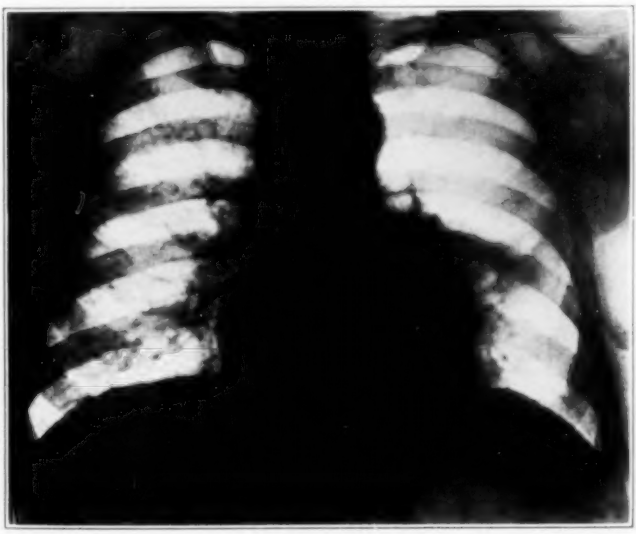

FIG. 2.—Case II. Obstructive emphysema of left lung due to bronchial compression from enlarged lymph nodes. Note the nodular enlargement at the root areas due to metastases from a pancreatic carcinoma to tracheobronchial lymph nodes.

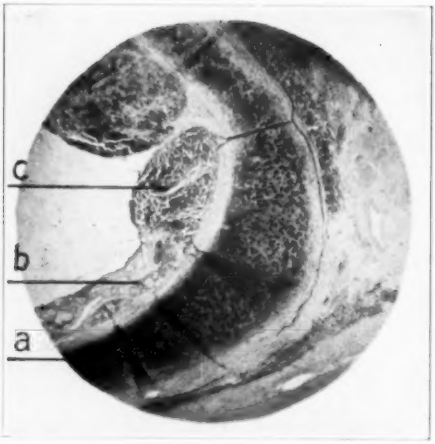

FIG. 3.—Case II. Direct invasion of bronchial wall by metastatic new growth (carcinoma of the pancreas): (*a*) bronchial cartilage; (*b*) normal bronchial mucosa; (*c*) replacement of mucosa by invading carcinoma.

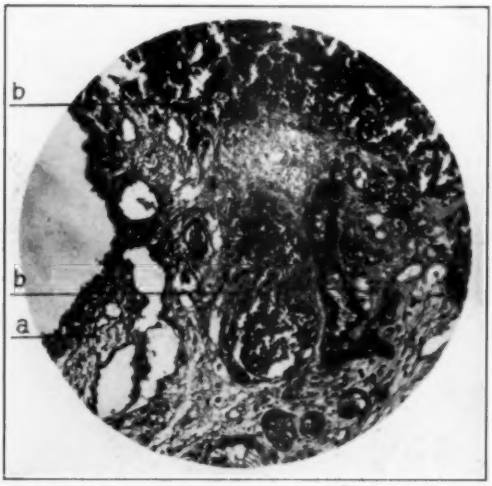

FIG. 4.—Case II. Higher magnification of bronchial mucosa seen in Fig. 3, showing the nature of the carcinomatous invasion: (*a*) bronchial mucosa; (*b*) carcinomatous areas.

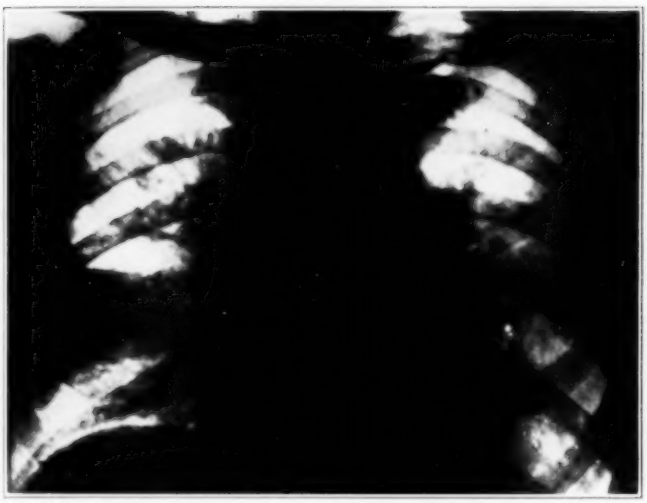

FIG. 5.—Case III. Area of increased density (abscess and consolidated tissue) middle portion of right lung, peripheral to a primary carcinoma of the right main bronchus.

FIG. 6.—Case IV. Showing the usual form of pulmonary metastasis from extra-thoracic new growth.

The Roentgen ray examination of the chest (Fig. 1) showed a rather large cavity in the right apex and another cavity in the lower portion of the right upper lobe with a definite fluid level. This was in fairly close relation to the root of the lung. These areas were thought to be lung abscesses. Bronchoscopy for diagnosis was done by Dr. L. H. Clerf on October 26. "The mucosa of the trachea, carina and right main bronchus was congested. The carina was somewhat broader than normal; the orifice of the right main bronchus was slightly compressed by the crowding inward of the right wall. At about the level of the middle-lobe bronchus, there were found small masses of tissue suggesting granulations which bled very readily when touched. Several small masses were removed for microscopic study. The lumen of the bronchus at this point was definitely constricted; it seemed rigid and fixed. No attempt was made to explore the bronchus beyond this point." The bronchoscopic diagnosis was stenosis of the right bronchus probably due to neoplasm of the right bronchus. Histologic examination of the tissue removed showed evidence of carcinoma and the conclusion, therefore, was carcinoma of the bronchus.

The patient lost ground very rapidly and died on November 6, 1927.

Necropsy (Dr. B. L. Crawford) showed that the right main bronchus was compressed by enlarged lymph nodes. There was a mass of these nodes in the mediastinum, on the right side of the trachea and along the right main bronchus. The nodes were firm and gray, and many measured several centimeters in diameter. The right upper lobe bronchus opened into a large cavity which communicated with several smaller ones, all occupying the upper lobe of the lung. Indurated lung tissue surrounded the cavities.

Examination of the abdomen showed a mass occupying the head of the pancreas. It was firm, grayish tissue which merged with pancreatic substance but could be easily differentiated. Similar nodules were found in the liver, the kidney and adrenals and on the surface of the large gut.

The anatomic diagnoses were: primary carcinoma of the head of the pancreas with metastasis to mesenteric, retroperitoneal, mediastinal and peribronchial lymph nodes and also to the liver, kidney, adrenals and colon. Abscess of the upper lobe of the right lung secondary to bronchial obstruction caused by enlarged lymph nodes.

Comment. This case illustrates how an abdominal tumor with metastases to mediastinal lymph nodes may cause bronchial compression producing symptoms and signs of chest disease which dominate the clinical picture. In the present instance, bronchoscopy with biopsy did not establish the secondary nature of the bronchial new growth. Moreover, even at postmortem up to the time that the primary new growth was found in the head of the pancreas it was thought that the cancer was primary in the bronchus.

In the second case the true state of affairs was early suspected and later definitely established; nevertheless, the signs of bronchial obstruction are interesting and the histologic features as demonstrated in the accompanying illustration furnish clear evidence as to the manner in which the bronchial wall may be invaded.

CASE II.—P. Z., aged forty-nine years, a white man, was admitted to the service of Dr. Thomas McCrae on February 13, 1928. He complained of cough, pain in the upper abdomen and middle of the back, and loss of weight. The family history was negative.

He had had good health except for a susceptibility to colds during the last

several years. He had pneumonia in 1922 from which he made a good recovery. The present illness began in November, 1927, at which time he was awakened one night with a sharp attack of pain in the epigastrium. He was not nauseated and did not vomit. He remained in bed for two weeks on a restricted diet and improved considerably. He then resumed work and continued until about two weeks before admission to the hospital at which time his pain returned. The pain came on about ten minutes after eating and lasted for about an hour or more. The pain was no longer restricted to the epigastrium but was likewise felt in the back.

During the last several weeks he had been increasingly distressed by cough and shortness of breath. He had lost 34 pounds in the last two and a half months.

Physical examination on admission to the hospital showed a fairly well-nourished patient with slight dyspnea, slight cyanosis and a tinge of grayish pallor. The scleræ were icteroid. There was marked infection of the gums. Examination of the throat and neck was negative.

Heart: The apex beat was not seen or felt but cardiac dullness seemed within normal limits. The sounds at the apex were distant but not abnormal.

Lungs: There was slightly lessened expansion at the left base. The percussion note anteriorly on the left was tympanitic, fremitus was decreased and breath sounds were almost entirely absent. Posteriorly the findings were the same. On the right side there were hyperresonance and exaggerated breath sounds.

Abdomen: There was rather marked tenderness and rigidity of the upper abdomen more marked on the right side and in the epigastrium. The spleen and the liver edge could not be felt although the liver seemed enlarged. The physical examination otherwise was negative.

The temperature was slightly subnormal; the pulse rate averaged 80; the respirations were slightly increased; and the blood pressure was within normal limits.

Within a week it was noted that the patient was losing ground rapidly and there was some evidence of jaundice which gradually deepened as time went on. Physical signs were not so pronounced over the left chest. There was some evidence that air was entering the lower lobe of the left lung and breath sounds could be heard a little better posteriorly. Rigidity of the upper abdomen became more marked. A tentative diagnosis was made of carcinoma in the upper abdomen, probably of the pancreas, with metastasis to mediastinal lymph nodes causing obstruction of the bronchus on the left side.

Laboratory studies other than the Roentgen ray gave no additional information.

The gastrointestinal studies (Dr. Leon Solis-Cohen) indicated possible carcinoma of the pancreas and Roentgen ray studies of the chest (Fig. 2) (Dr. John T. Farrell, Jr.) showed a distinct nodular enlargement at each root area. The masses were fairly sharply circumscribed and were thought to be due to the enlargement of the lymph nodes. There was a distinct difference in the aëration of the two sides of the chest, which was very pronounced on fluoroscopic study. It was noted that the right diaphragm moved freely while the left moved practically not at all, and with expiration the heart was displaced to the right. These changes indicated an obstructive emphysema of the left lung due probably to compression of the bronchi.

The patient rapidly grew worse and died on April 22, 1928.

Necropsy demonstrated a large primary carcinoma of the pancreas with metastasis to tracheobronchial lymph nodes. Near the bifurcation of the main bronchus of the left lung there was invasion of the bronchial wall (Figs. 3 and 4) producing marked stenosis.

The third case illustrates the second point mentioned in the introduction, that is, how confusion in diagnosis may be brought about by the extrathoracic metastases of primary bronchial carcinoma.

CASE III.—J. V., a white man, aged forty-seven years, was admitted to the service of Dr. Thomas McCrae, March 24, 1928. He complained of cough, expectoration, pain in the right chest, loss of weight and strength. The family history was negative. The patient stated that he had always enjoyed good health. He used tobacco and alcohol moderately. He had lost about 30 pounds in weight in the last five or six weeks.

The present illness began about five months before admission to the hospital with cough and expectoration. The expectoration at first white gradually increased in quantity and became yellowish. Occasionally the sputum was blood streaked. Later the patient vomited with the attacks of coughing. For a few days before admission he noted some swelling of his feet and ankles.

Physical examination on March 28 showed a very well-developed but poorly-nourished patient who was markedly dyspneic, and slightly cyanotic. There was no clubbing of fingers. The face and neck were rather red and this redness was increased by cough. The cervical lymph nodes on both sides were moderately enlarged. There seemed to be some fixation of the larynx but no tracheal tug. There was slight distention of the veins of the upper chest and a rather distinct costal fringe of capillaries. The heart was within normal limits and the sounds were normal.

The chest expansion was generally diminished but especially so on the right side. The percussion note on the right side was tympanitic with a sort of wooden tympany over the apex and in the first and second interspaces. The breath sounds were much diminished. On the left side the percussion note was hyperresonant and the breath sounds were exaggerated. Parasternal dullness seemed increased in the first and second interspaces on both sides. Posteriorly the findings were the same, that is, hyperresonance and exaggerated breath sounds on the left; tympany and absent breath sounds over the upper right chest and distant breath sounds over the lower right chest. Abdominal examination showed a large mass occupying the epigastrium both to the right and left of the umbilicus which seemed as though it might be connected with the liver. The remainder of the physical examination was negative.

A tentative diagnosis was made of abdominal new growth with metastasis to the mediastinum and neck, obstructive emphysema of the right upper lobe due to bronchial compression from lymph-node enlargement and probable secondary infection of the right lower lobe.

The temperature was 101° on admission, the pulse 110 and the respirations 32. The blood pressure was 135 systolic and 60 diastolic.

Roentgen ray examination of the chest (Fig. 5) showed an area of increased density in the middle portion of the right lung. There was marked thickening of the root shadows on the right side. The Roentgen ray interpretation was malignant metastasis with enlargement of mediastinal lymph nodes. The gastrointestinal tract showed no evidence of malignancy, and gall-bladder function as determined by the cholecystogram was normal. The van den Bergh test gave a slightly positive indirect reaction. The blood Wassermann was negative. The blood count was nearly normal. Repeated sputum examinations were positive for blood but failed to show tubercle bacilli. Urine studies were essentially negative.

Bronchoscopic examination by Dr. L. H. Clerf on March 31 revealed "marked compression of the lower end of the trachea; the carina was compressed from before backward, so that the anterior and posterior extremi-

ties were practically on the same plane and its edge could be seen only on deep inspiration. The orifices of both main bronchi, especially the right, were smaller than normal; the angle of bifurcation of the trachea was widened; the right main bronchus showed a definite stenosis, apparently the result of infiltration of the bronchial wall. There was considerable rigidity of the right bronchus and its lumen was triangular in appearance. The mucosa was intensely inflamed, granular, and bled slightly when touched. A moderate quantity of purulent secretion was aspirated from the right bronchus. The bronchoscopic diagnosis was compression stenosis of the trachea and right bronchus; widening of the angle of tracheal bifurcation. The bronchial findings suggested the presence of large tracheobronchial lymph nodes producing compression of the lower end of the trachea and infiltration of the right bronchus."

The patient grew worse rapidly and died on April 13 from pulmonary edema.

Necropsy showed a primary carcinoma of the right main bronchus producing marked constriction of its lumen. There was an abscess of the upper portion of the lower lobe about 3 cm. in diameter and an area of consolidation in the lower portion of this lobe. There was marked involvement of the mediastinal lymph nodes. The liver weighed 4100 gm., being the seat of numerous large metastatic nodules.

In this case huge enlargement of the liver due to metastases from a bronchial carcinoma misled me into believing that the primary new growth was in the abdomen and that the secondary lesion was in the lung.

In the fourth case we again suspected that an abdominal new growth had metastasized to the lung and in this instance although autopsy was not obtained the Roentgen ray of the chest quite definitely established the correctness of this view.

CASE IV.—S. G., aged forty years, an adult, white male, was admitted to the service of Dr. Thomas McCrae on March 1, 1928. He complained of shortness of breath; cough and expectoration; and pain on the right side of the abdomen. The past history revealed no serious illness apart from frequent sore throats. The present trouble began five weeks before admission to the hospital with an illness diagnosed as grippe. He had pain on the right side, cough, and later, expectoration and shortness of breath. He had been in bed off and on since that time. There had been very little loss of weight.

The physical examination on admission to the hospital showed a well-developed, well-nourished patient who was quite dyspneic and looked very ill. Examination of the chest showed general restriction of expansion, more marked on the right side. The percussion note on the right side was tympanitic above and impaired below, and over the area of tympany the breath sounds were diminished. The left side throughout was hyperresonant and the breath sounds were exaggeratd.

Examination of the abdomen showed a mass on the right side which roentgenologically did not seem to be connected with the gastrointestinal tract, nor did it seem connected with the liver. It was thought that it probably arose from the right kidney and a tentative diagnosis of probable hypernephroma was made although blood never was found in the urine. The chest signs were interpreted as due to metastasis from this abdominal new growth and the Roentgen ray confirmed this opinion (Fig. 6).

The patient died at home the following month and no autopsy was obtained.

Comment. Among the many difficulties encountered in the diagnosis of primary carcinoma of the bronchi the domination of the clinical picture by an abscess of the lung peripheral to the new growth deserves prominent mention. Another difficulty spoken of by various authors concerns metastases from a small primary bronchial carcinoma to other organs producing striking manifestations of disease in these other organs and thus obscuring the diagnosis of the primary new growth. A third important diagnostic consideration works in exactly the opposite manner. Metastases from extrathoracic new growths to the parenchyma of the lungs have long been known and increasingly recognized with the wider use of the Roentgen ray. Little attention has been paid, however, to the metastases from extrathoracic new growths to tracheobronchial lymph nodes causing enlargement of these nodes, compression of the bronchi and in this manner producing signs and symptoms of pulmonary disease. Under such circumstances, the evidences of pulmonary disease may dominate the clinical picture, and lead one to believe that the primary new growth is bronchial in origin.

Bronchial compression brought about by enlargement of peribronchial lymph nodes is capable of producing an obstructive emphysema as shown in accompanying plate from Case II.

Obstructive emphysema of foreign body origin is well known, particularly in children and usually is readily recognized. Here ball-valve action of the foreign body in the bronchus permits air to enter a portion of the lung but does not allow it to leave, and in this manner varying grades of overdistention of the lung are produced. Bronchial compression brought about by pressure of large lymph nodes probably acts in a somewhat similar manner. It would seem that air enters the partially closed bronchus successfully but due to narrowing of the bronchus on expiration finds difficulty in leaving and that portion of the lung supplied by the partially obstructed bronchus remains overdistended for a varying period of time. When complete closure of the bronchus occurs the air from that portion of the lung is absorbed and atelectasis results.

The signs of obstructive emphysema are usually distinctive. There are deficient expansion, tympanitic percussion note and diminished or absent breath sounds over the affected area. The signs may vary from time to time as influenced by rest, by progression of the bronchial compression, or by retained secretions. It is important to remember that over the unaffected lung one is apt to obtain hyperresonance and exaggerated breath sounds due to the compensatory overexpansion. For this reason, the error has been made of considering a lesion to exist on the sound side.

The necessity for differentiation from pneumothorax or collapse of the lung may arise. In pneumothorax as in obstructive emphysema one may obtain a tympanitic percussion note and diminished or absent breath sounds over the affected area, and the displacement phenomena of pneumothorax may not be sufficiently pronounced

to be of aid in diagnosis. One is not so apt to be confused by collapse of the lung, as here one usually obtains a dull percussion note over the affected area and the displacement of the heart toward the involved side is an important and usually a striking feature of the condition. Other findings such as a positive coin test in pneumothorax and the febrile reaction of collapse together with the history and the evidence disclosed by the Roentgen ray will probably be sufficient for ready differentiation.

Conclusion. There is often considerable difficulty in differentiating primary and secondary carcinoma of the bronchi for the reason that extrathoracic new growths may metastasize to and cause enlargement of tracheobronchial lymph nodes, producing bronchial compression, so that chest symptoms and signs dominate the clinical picture. These secondary growths may actually invade the bronchial wall in such a manner that bronchoscopist and microscopist likewise may be confused with regard to the point of origin of the new growth.

It is important to differentiate primary and secondary carcinoma of the bronchi because early recognition and prompt treatment of primary bronchial carcinoma offers some hope from the standpoint of improvement and possible cure.

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SPONTANEOUS NONRHYTHMIC VARIATIONS IN THE BLOOD-PRESSURE LEVELS AND IN THE "SILENT GAP."

A Theory of Vasomotor Arrhythmia.

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That blood pressure occasionally undergoes spontaneous variations without any detectable cause was known for a long time. Janeway[1] mentioned four forms of variations that occur in experimental animals—more rapid, cardiac; larger, respiratory; longer and slighter, Traube-Hering and spontaneous nonrhythmical variations, which may be reflex or due to change in the central nervous system. He added that these periodic variations are evident in the human as well as in animals, but doubted if such variations are ever higher than 30 mm. of mercury.

No reference could be found in the literature, however, of the extent and nature of spontaneity in blood-pressure variations and

its possible explanation and significance. In an attempt to determine these factors, I made a study of 100 patients, 72 of whom had normal or subnormal pressures and 28 hypertensives. The method of procedure was to have the patient in a dorsal recumbent posture, head and upper part of the body somewhat elevated by support, such as that offered by the ordinary Isaacs table, to give more comfort and rest. The examining room was isolated from any outside disturbances, as far as possible, and the patient was allowed to remain at rest for three to five minutes before determinations began. The pulse rate was then taken the first fifteen seconds and the systolic and diastolic readings during the rest of the minute, determinations being made every minute for periods of ten to twenty-five minutes. Each patient's readings were tabulated in order, the pulse rate per minute having been determined by multiplying the rate in fifteen seconds by four.

Of the 72 patients with normal or subnormal blood pressures, 50 showed practically no variations in the pressure levels or only such slight variations as would be explained by respiratory activity. Nineteen showed variations of 10 to 20 mm. and 3 of more than 20 mm., but not higher than 30 mm. Of the 28 hypertensive patients, on the other hand, 12 showed variations of 10 to 20 mm., 13 of 20 to 30 mm. and 3 of 40 mm. or higher. In some cases the systolic pressure level fluctuated most, in others the diastolic, as shown in Table and Fig. 1.

TABLE I.—FLUCTUATIONS IN BLOOD PRESSURE OF A FEMALE WITH PRESSURE WITHIN NORMAL LIMITS.

		Blood pressure.	
Minute.	Pulse rate.	Systolic.	Diastolic.
1	80	124	96
2	80	126	102
3	70	120	78
4	80	130	90
5	80	122	90
6	78	128	90
7	80	122	94
8	78	120	86
9	74	116	88
10	72	120	90
11	80	118	90
12	80	120	90
13	78	120	96
14	72	118	96
15	76	118	92
16	76	123	90
17	76	122	88
18	76	118	86

These readings were obtained from a female, aged twenty-seven years, whose blood pressure was within normal limits. Her complaints were shifting body pains, slight shortness of breath on walking two flights of stairs and constipation. She was obese, weight being 173 pounds, height 62 inches. Her heart and lungs

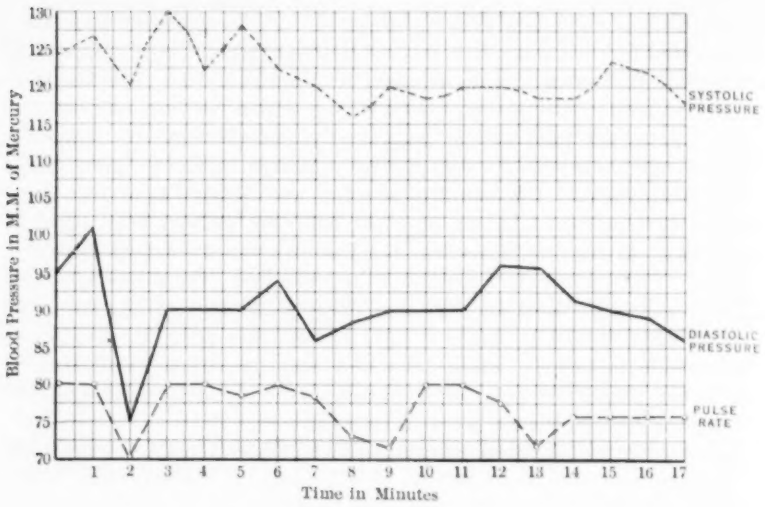

FIG. 1.

were negative. She had chronically infected tonsils with a history of repeated attacks of tonsillitis. The difference between her maximum and minimum systolic readings was 14 mm., while that of the diastolic was 24 mm. The pulse pressure was 22 to 45, comparing extremes. There is a disproportion in the fall and rise of the pressure levels.

TABLE II.—FLUCTUATION IN BLOOD PRESSURE IN HYPERTENSION.

		Blood pressure.	
Minute.	Pulse rate.	Systolic.	Diastolic.
1	84	184	120
2	84	164	124
3	76	170	128
4	80	204	120
5	76	210	120
6	80	204	114
7	80	160	110
8	72	200	118
9	74	210	120
10	72	204	130
11	76	204	120
12	76	210	120
13	74	190	128
14	74	210	116
15	76	200	120
16	74	206	120
17	76	200	100
18	76	204	130
19	74	204	120
20	72	204	140
21	72	212	140
22	72	200	120
23	70	204	150
24	72	204	120
25	76	194	112

In the hypertensive the fluctuations seem to vary with the type of hypertension. The individual presenting periodic changes in blood pressure, as described in a previous paper,[2] seems to show greater fluctuations than the one whose pressure is permanently high. This is shown in Fig. 2 and Table 2 obtained from a female,

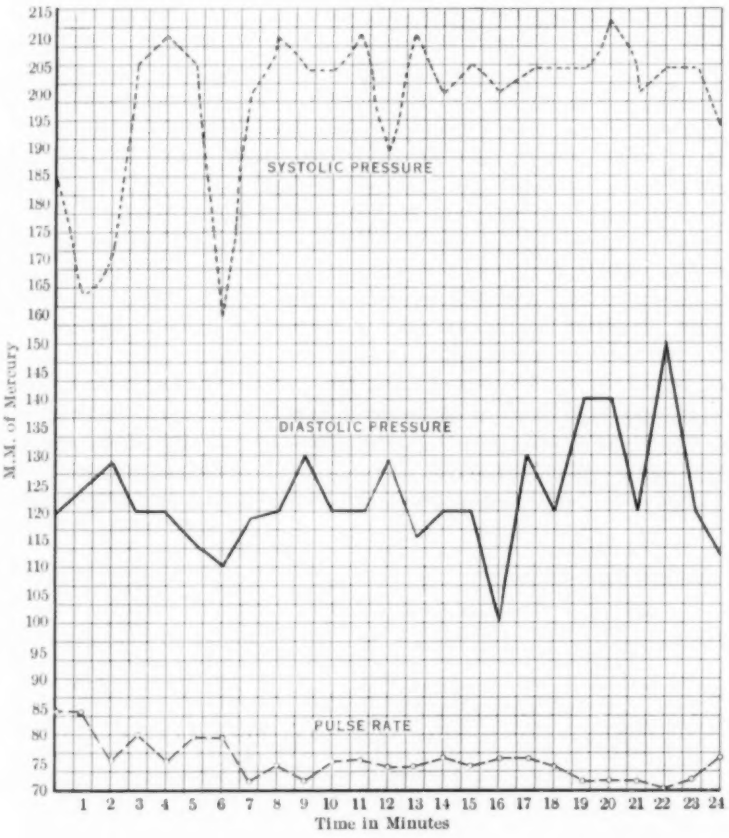

FIG. 2.

aged fifty-eight years, who, aside from vague aches and pains, felt well. She presented hypertension with marked periodic remissions. As is noticed, her systolic pressure level shows marked fluctuations the first eight minutes and lesser ones during the rest of the observation. The diastolic level shows greater fluctuations the latter part of the observation. There is no correspondence between the systolic and diastolic curves. The maximum systolic reading is 212 mm. and the minimum 160 mm., making a difference of 52 mm. The maximum diastolic reading is 150 mm. and the minimum 100 mm., making a difference of 50 mm. The pulse pressure, is as low as

50 mm. at the sixth minute and as high as 100 mm. at the sixteenth minute.

TABLE III.—SIMILAR FLUCTUATIONS IN A HYPERTENSIVE ON TWO OCCASIONS.

	Blood pressure.			
	Systolic.		Diastolic.	
Minute.	8/10/27	9/17/27	8/10/27	9/17/27
1	178	180	104	110
2	150	195	90	100
3	154	194	92	100
4	152	198	96	96
5	154	190	90	94
6	176	186	90	98
7	168	190	92	96
8	180	186	94	96
9	178	190	90	100
10	168	168	96	100
11	175	174	98	
12	158	...	92	
13	180	...	94	
14	180	...	90	
15	158	...	90	
16	164	...	98	

An interesting feature observed in two hypertensive cases is that the extent of fluctuations was the same on two different occasions in the same individual, under varying levels of blood pressure. The findings of 1 of these cases are shown in Fig. 3 and Table 3, obtained

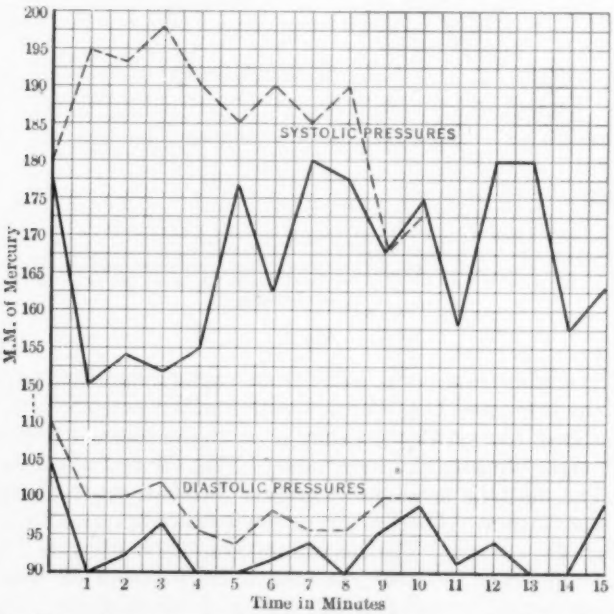

FIG. 3.—Heavy lines represent blood pressure on August 10, 1927. Broken lines represent blood pressure on September 17, 1927.

from a female, aged fifty-seven years, who was mildly diabetic and hypertensive. Aside from some pain in the right shoulder, she had no other complaints. Her blood pressure on August 10, 1927, was maximum systolic 180 mm. and minimum 150 mm., making a difference of 30 mm. The maximum diastolic was 104 mm. and minimum 90 mm., making a difference of 14 mm. On September 17 the maximum systolic was 198 mm. and minimum 168 mm., making a difference also of 30 mm., while the maximum diastolic was 110 mm. and minimum 94 mm., making a difference of 16 mm.

In the chronic hypertensive individual, whose blood pressure is persistently high and who shows definite anatomic, cardiovascular changes, the fluctuations are comparatively slight. This is illustrated in Fig. 4 and Table 4, representing the findings of a male, aged fifty-five years, who for the past ten years was known to have had hypertension. He developed a sudden left hemiplegia two years ago, of mild degree, lasting two days. His chief complaints were precordial pain on exertion, moderate dyspnea and frequent pain in the back of his head and neck. He was obese, markedly arteriosclerotic, with some exophthalmos and edema of the lids. His heart was greatly hypertrophied and the aortic arch was found to be markedly widened under the fluoroscope. The heart sounds were strong, booming, with accentuation of the aortic second sound. No murmurs were heard. His urine and blood chemistry examinations were negative, as was the blood Wassermann test. He died from cerebral hemorrhage.

TABLE IV.—SLIGHT FLUCTUATIONS IN A CHRONIC HYPERTENSIVE.

	Blood pressure.			
Minute.	Systolic.	Limits of gap.		Diastolic.
1	220	195	180	130
2	220	215	190	120
3	220	195	175	120
4	218	208	170	130
5	208	200	180	130
6	224	200	174	120
7	208	190	160	120
8	214	210	180	130
9	215	205	170	125
10	210	200	180	125
11	220	190 W.	170	130
12	215	190	160	130
13	205	190	170	130
14	210	190 W.	170	130
15	210	190	170	130

This patient showed a "silent gap" in his blood pressure—a term designating the temporary disappearance of the sounds heard during the course of auscultatory examination of the blood pressure. It is

elicited by the gradual deflation of the air bag and carefully listening for the appearance of the regular, rhythmic sounds indicating the systolic blood-pressure level. On further gradual lowering of the pressure in the bag, the sounds are found to disappear for a certain number of millimeters, only to return again and persist until the permanent diastolic disappearance of the sounds occurs. For example, assuming that the systolic level is found to be at 180 mm.,

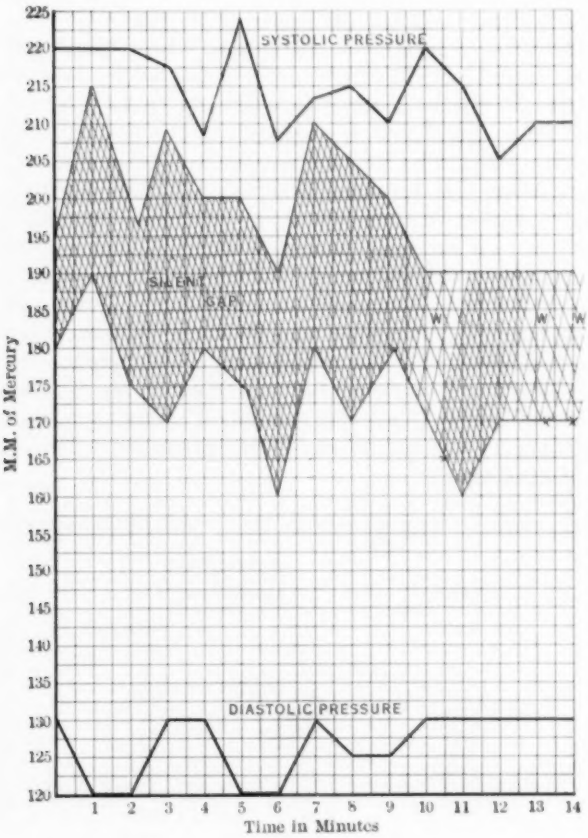

FIG. 4.

the sounds will continue to be heard for several millimeters, say down to 170, when they will disappear for a varying number of millimeters, say down to 150, after which they will be heard again to the true diastolic level, say of 100 mm. The length of time for the disappearance of the sounds varies in different cases.

The condition was first described, according to Gibson,[3] by the French writer, Tixier, who thought it to be present only in some

cases of mitral stenosis. Gallavardin, according to the same author, named the phenomenon "trou auscultoire," and stated that he met it in other conditions than in mitral stenosis. I first observed this phenomenon in a case of aortic insufficiency at the cardiac clinic of the New York Post Graduate Hospital, before I knew of its existence from the literature, and thereafter watched for it in all cases in which blood-pressure determinations were done for any length of time. I found the condition to be comparatively rare, and to occur occasionally in the hypertensive individual, particularly in the chronic and graver form. I also found that just as the systolic and diastolic levels may fluctuate, so may the upper and lower limits of the gap.

This is well illustrated in the figure and table of findings of the patient under discussion. As will be seen, the systolic and diastolic levels fluctuate comparatively little, while the fluctuations of the gap are more marked. The maximum and minimum limits of the gap are 215 mm. and 160 mm. respectively, at an interval of five minutes. The nearest interval between the systolic level and the upper gap level in the same interval of time is 4 mm. in the seventh minute, and the farthest is 30 mm. in the tenth minute. Here, however, as in the thirteenth and fourteenth minutes, there is no complete gap in the sound, but a weak sound (W) could be heard, continuous from the systolic beginning to the diastolic end. The lower level of the gap is further from the true diastolic pressure than the upper is from the systolic. Thus, in the first minute it is as long as 70 mm., while in the eleventh minute it is 30 mm.

TABLE V.—OCCURRENCE OF THE SILENT GAP.

Minute.	Blood pressure.			
	Systolic.		Diastolic.	
1	190	...	...	140
2	190	...	...	145
3	180	...	...	145
4	190	...	...	142
5	206	...	...	140
6	210	200	160	140
		Gap		
7	220	200	160	140
8	220	...	...	150
9	220	200	175	140
		Gap		
10	220	200	160	140
		Gap		
11	220	200	150	140

Another peculiarity observed about the gap is that it may occasionally occur for two or more successive minutes or even in isolated

determinations, disappear and reappear again. This is shown in Fig. 5, and Table 5, obtained from a female, aged twenty-eight years, suffering from chronic pyelonephritis of four years' standing. The condition followed pregnancy which was associated in the sixth month by uremic manifestations and spontaneous delivery. She was unconscious at that time for four days, following repeated convulsions. Since then her condition has been that of recurring semi-invalidism. Pus, albumin, various forms of casts are constant urinary findings, and the blood pressure ranges between 180 and 220 mm. systolic and 140 to 150 mm. diastolic. As will be noticed from the figures, there was no gap the first four minutes, during

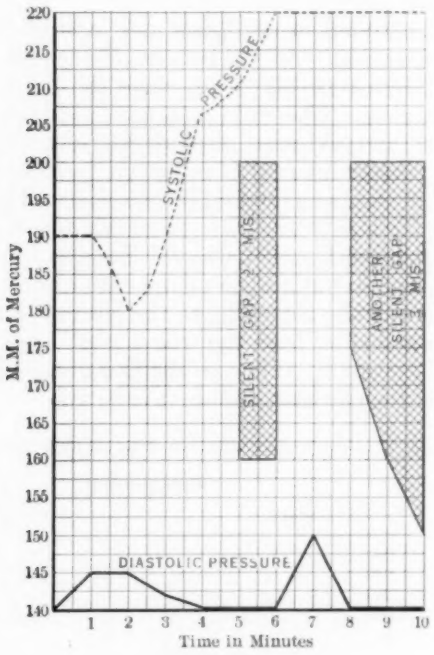

FIG. 5

which time the systolic blood pressure ranged between 180 and 205 mm. At the fifth minute the systolic pressure mounted to 210 mm., with a gap appearing between 200 and 160 mm. At the sixth minute the systolic level rose to 220 mm., the gap remaining the same. During the seventh minute no gap was present, and the diastolic level was higher. In the last three minutes there were no fluctuations in either the systolic or diastolic levels, but the gap gradually grew larger.

Discussion.—The important facts to be considered in the observations presented in this paper are: (1) That in some individuals

with normal blood pressures the systolic and diastolic levels fluctuate apparently spontaneously; (2) that in the hypertensive individual showing periodic remissions such fluctuations are the rule and are very prominent; (3) that in the chronic, nonremittent form of hypertension in which anatomic cardiovascular changes are marked, the fluctuations are less prominent, but a silent gap in the sounds may occur; (4) that every level of blood-pressure reading fluctuates independently of the other and in a disorderly fashion; (5) that the extent of the fluctuations seems to be approximately the same on different occasions, even if the blood-pressure readings are not the same.

Physiologic Considerations. In an attempt to explain these phenomena, a brief consideration of the mechanism of blood-pressure production and maintenance is necessary.

The factors concerned in this mechanism are the heart energy, the elasticity of the vessel walls, the volume of circulating blood and the peripheral resistance. Of these, the peripheral resistance is the dominant factor in initiating *changes* in blood pressure when the person is physically at rest. Exceptions are when variations in the heart activity occur, such as is found in auricular fibrillation and pulsus alternans. Also such results may follow deep breathing with its mechanical effect of thoracic aspiration and reflex vasomotor effect, as has been shown by some investigators, such as Erlanger and Festerling[4] and Lewis.[5] Such conditions are, however, excluded from our discussion.

The greatest factor in the production of peripheral resistance is tonus of the vessel walls, for though the resistance produced by the branching of the arteries and by internal friction due to the viscosity of the blood are also factors, such are negligible from a variability viewpoint. It is the constant change in the tonus of the arteries, arterioles and capillaries, especially in the splanchnic circulation, that produces its changing effect on the general blood pressure. Such tonus is maintained by the vasoconstrictor nerves, having their main center in the medulla and some subsidiary centers in the spinal cord. Increased activity of the center produces vasoconstriction with a rise in pressure, decreased activity produces vasodilation with a fall.

Under various states of emotional and physical activity such increase or decrease is produced by an increase or a decrease in the impulses reaching the center through various afferent channels. In conditions of rest, such as in our observations, any variation in activity of the vasoconstrictor nerves must be due either to spontaneous variations in activity of the vasomotor center or of the efferent vasoconstrictor nerves or of both. In other words, we must assume here the existence of an automaticity in the vasoconstrictor nervous mechanism which undergoes constant spontaneous changes independent of any change in the extrinsic nervous influences, the

extent of which varies with the individual. In most normal persons there is a stability of this mechanism with an established level of tonicity, yielding little variation, except reflexly. In some cases, however, there seems to be more or less fluctuation in this vasomotor tone, nonrhythmic in nature, to which the name "vasomotor arrhythmia" may be applied, and to which the physiologic homologue of sinus arrhythmia can be compared. Like the latter, which was shown by Mosler[6] to have no periodicity in its variations nor constant relationship to the rhythm of respiration, this arrhythmia is similarly characterized. It seems to be most pronounced in some of the benign hypertensive individuals.

As to the underlying cause of this arrhythmia, nothing but conjectural assumptions can be made. We may assume a lability of the vasomotor center in the medulla caused by some chemical substance, metabolic or toxic, which produces various grades of stimulation and depression from moment to moment. It is more likely however, that local variations in the blood supply to the medulla from moment to moment, such as would be caused by local vascular spasm, may be the underlying factor. It is a long-recognized physiologic law that diminished blood supply to the medulla results in a compensatory rise in the systemic blood pressure. This has been proved by Starling, who suggested claudication of the center vessels as a cause of hypertension. Cushing[7] proved the effect of cerebral anemia on rise in the systemic blood pressure by his experiments in cerebral compression and decompression on animals and in some of his clinical cases. Boardley and Baker[8] investigated the arterial changes in the medulla in 14 cases of arteriosclerosis with hypertension and in 10 cases of arteriosclerosis without hypertension and found that in the hypertensive the medullary blood vessels were invariably involved in sclerotic changes while in the others they were not.

We may infer from these facts that in certain individuals there is a local vasospasm of the vessels of the medulla producing some anemia of the vasomotor center with a resulting rise in the general systemic blood pressure. This rise results in an increased blood supply to the center, producing a fall, soon to rise again when the fall is sufficient to produce more or less anemia of the center. This process is apparently continuous and occurs independent of any reflex condition.

The explanation of the "silent gap" encountered in some individuals is difficult. It may perhaps correspond to the fifth phase, or the so-called "phase of friction sound" of Brooks and Bleile,[9] representing the period during which the blood passes through a slit-like opening of the partially compressed artery. How the sounds disappear is hard to understand.

Value of the Observations. The practical value of the observations presented in this paper is twofold: (1) It will teach us to avoid

the formation of too hasty conclusions in the observation and treatment of blood-pressure abnormalities; (2) it may throw some light on the causation of hypertension.

The first factor is appreciated when we realize how often conclusions are drawn from an occasional observation on the results of treatment or of environmental changes, producing presumably a drop in blood pressure. We only have to refer to the conflicting results reported by various observers on the effect of change in posture, for instance, on blood pressure or of certain drugs and methods in the treatment of hypertension, to see that spontaneity in blood-pressure changes is probably the underlying cause of such differences. To evaluate properly any method, a knowledge of the individual "normal" fluctuations must be had first. Only then can we judge if any change is due to the method.

Of greater value in the appreciation of these fluctuations is the possibility of associating them with the causation of hypertension, thus paving our way for a better understanding of that phenomenon. In view of the greater frequency and prominence of the occurrence of fluctuations in the benign hypertensive individual, we may conceive of vasomotor arrhythmia as being the cause of hypertension. Further observations will probably reveal the following stages in the development of the persistent form of hypertension: First stage, that of comparatively mild fluctuations seen in individuals presenting normal blood pressures. Second stage, that of greater fluctuations with an occasional rise above normal limits. Third stage, when the adaptations of the blood supply to the medullary vasomotor center becomes poor, due to increased spastic state and to some sclerotic changes of the vessels there, producing more prolonged periods of hypertension. Fourth stage, when as a result of the hyperactivity of the medullary blood vessels, marked sclerosis of these vessels has taken place, resulting in a permanent anemic state of the vasomotor center, with the resultant permanently high blood pressure, with comparatively slight fluctuations. The cases presented in this paper illustrate this conception fairly well, and it remains to be shown if those individuals with normal blood-pressure readings who show such fluctuations are the ones that will eventually develop hypertension, I am inclined to believe that such will be found to be the case.

Summary. A study of the pulse rate and blood pressure of 100 patients was made at minute intervals, for periods of ten to twenty-five minutes. Of 72 patients with normal blood pressure, 50 showed practically no fluctuations in their readings from minute to minute, 19 showed variations of 10 to 20 mm. and 3 of over 20 mm., but not higher than 30 mm. Of 28 hypertensive cases, 12 showed variations of 10 to 20 mm., 13 of 20 to 30 mm. and 3 of 40 mm. or higher. The greatest fluctuations occurred in hypertensive individuals showing periodic remissions. In some of the severe hypertensive cases a

"silent gap" in the sounds was found, the levels of which showed independent fluctuations.

A theory of "vasomotor arrhythmia" is offered to explain this phenomenon. The theory assumes a disturbance in the discharge of rhythmic vasomotor impulses from the medullary vasomotor center, caused by local anemia there, such as would be produced by angiospasm or the like.

Based on these findings, the pathogenesis of hypertension is suggested as occurring in four stages: (1) In an instability of the normal blood pressure; (2) in an occasional rise of the pressure to above normal levels; (3) a more frequent occurrence of hypertension, with deeper fluctuations of blood-pressure levels, as a result of some added structural vascular changes in the medulla to those of functional changes; (4) the production of definite anatomic changes in the vessels of the medulla, resulting in more or less permanent rise in blood pressure, with smaller fluctuations.

Conclusions. Certain individuals have persistent fluctuations in their blood-pressure levels even under conditions of rest. Such fluctuations are most prominent in hypertensive individuals showing periodic variations, but occur also to a less extent in all other hypertensive cases, and in some cases with normal blood pressure. Because of its constant occurrence in hypertensive cases, and its occasional presence in normal blood-pressure cases, we may consider such latter cases as heading toward hypertension. To explain persistent fluctuations in pressure, we must assume a disturbance in the rhythmic vasomotor discharges that normally maintain the blood pressure at a constant level when the person is at rest, and a sort of "vasomotor arrhythmia" to set in. The recognition of the existence of such "normal" fluctuations will avoid the mistaken belief in the potency of some therapeutic factors, or in the efficiency of some blood-pressure tests.

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ACUTE MASSIVE (NONSURGICAL, NONTRAUMATIC) PULMONARY ATELECTASIS.

Report of Two Cases.

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Since 1890, when Pasteur first described pulmonary atelectasis, which he found in association with postdiphtheritic paralysis of the diaphragm, it has been described by other observers in association with various disturbances, largely following surgery or traumatism.

Although internists have seen and recognized this condition as a definite clinical entity in surgical patients, it would appear from the literature that, except to state that it occurs in purely medical conditions, relatively few have described its actual occurrence.

Pasteur, in 1914, reported 16 cases of massive collapse in a series of 201 postoperative complications. Jackson and Lee[1] state that 48 cases have been recorded in the literature since Pasteur's observations in 1914, that Scott in January, 1915, had collected 64 cases and reports that he had access to 12 unpublished records of cases. Norris and Landis[2] state that massive collapse of the lung occurs as a complication of pneumonia. Rose Bradford[3] reports an autopsy of such a case. Tidy[4] reports a doubted case of massive collapse of the entire right lung in the case of diaphragmatic pleurisy. Chevalier Jackson[5] reports a very large experience with collapse of a part or of the entire lung as a result of the lodgment of foreign bodies in the bronchi. Pasteur saw lobar collapse of bases of the lung in pleurisy, apical pneumonia and hydrochloric acid poisoning. Collapse of the lung was reported by N. Kletz[6] complicating an attack of acute meningitis. Massive collapse complicating a case of abscess of the lung was reported by Elwyn.[7] Regan[8] records a case of collapse of lung in a case of acute poliomyelitis. Wallgren[9] found collapse of the lung in 8 cases of pneumonia in children, with displacement of the heart toward the affected side, all of which recovered. Gwyn[10] states that collapse of the lung was diagnosed in 3 cases; 2 suffered from lobar pneumonia and 1 from a respiratory infection, in all probability also pneumonia.

Etiology. Different theories as to its cause have been advanced but none has met with general approval. Jackson and Lee,[11] after a careful analysis of many diverse conditions with which massive collapse is associated, show two factors to be constant; (1) obstruction of the bronchial tree, which is followed by the absorption by the pulmonary circulation of the air imprisoned in the alveolar tissue distal to the obstruction; (2) some interference with the respir-

atory movements. This interference may be partial or complete but always results in decreased aëration of the pulmonary tissue on the involved side.

Scott[12] believes that spasm of the bronchiole, or a vasomotor disturbance resulting in the swelling of mucous membrane similar to angioneurotic edema are possibilities in causing massive collapse of the lung. Until more direct evidence of the cause and effect are produced, the theory of bronchial obstruction with some interference in respiratory movement seems most plausible.

Autopsy performed upon patients showing massive collapse of the lung at times fails to show mechanical obstruction of the bronchial tree. It must be borne in mind that considerable rough handling and twisting of the lungs takes place in the course of their removal from the body, and may readily dislodge the obstruction. Pulmonary edema, labored breathing with cough often occurring for a varying number of hours before death, may be factors in dislodging obstructions of the bronchi by mucus or secretions acting as plugs.

Jackson states that following the removal of a foreign body from the bronchus the lung becomes air-containing slowly, usually twelve to forty-eight hours elapsing before it becomes fully expanded. He also finds that when a new growth in the bronchus completely occludes the entrance of air to that lung, pulmonary atelectasis occurs. Removal of the tumor allows air to reënter and the lung expands.

Lee, Tucker and Clerf,[13] from the 30 cases of postoperative massive atelectasis whose records they have been able to study, are persuaded that two factors have been constant in practically all in this group: (1) a thick, viscid bronchial secretion, and (2) some inhibition of coughing. Because of the thick, tenacious character of this bronchial secretion and the inability or disinclination of the patient to clear it from the bronchi, it accumulates in the dependent portion of the bronchial tree until, at some point or points this stream of mucus completely occludes the lumen. These observers report the production of atelectasis of lungs in dogs after an injection into the bronchus of material removed from a patient suffering from this condition.

Lee, Tucker, Ravdin and Pendergrass[14] state that the use of material removed from a clinical case to produce pulmonary atelectasis had not been reported prior to the work of Lee, Tucker and Clerf. They believe that the failure to reproduce this condition has been due to the inability to control the cough reflex. Their experiments consisted of preparing a solution of acacia, giving a dog a general anesthetic, preceded by hypodermic injection of morphin and perforating an exploratory laparotomy following which sodium amytol was given intraperitoneally to inhibit the cough reflex. Roentgen ray examinations of the chest made before and

after the introduction of the acacia solution into the bronchus by means of a bronchoscope and again following its aspiration from the bronchus showed that when the cough reflex was abolished atelectasis of the lung was produced and that the removal of the acacia solution by bronchoscopic aspiration caused the lung to reëxpand.

Symptoms. On account of the symptom complex differing from all others present in pulmonary disturbances, it is most important to be fully informed as to the symptomatology.

The condition is usually sudden in onset. Dyspnea and cyanosis are obvious upon inspection. The patient is usually not toxic and recovers in from two to four weeks. Associated conditions may cause toxemia and death. There is a very definite and sudden increase in the respiratory rate reaching up to 40 or 50 a minute. Fever ranging from 100° to 104° F. accompanies the condition. The polymorphonuclear leukocytes are increased, ranging from 10,000 to 20,000. The cough may be short, hacking and nonproductive early, later becoming productive in character. In one of our patients, the cough began immediately after the onset of the collapse and for a week the sputum was blood tinged.

The dyspnea, cough and cyanosis may cause the patient, who, though not toxic, to appear ill. His expression denotes anxiety. Bronchopneumonia may complicate collapse of the lung. It is believed that bronchopneumonia frequently develops in collapsed areas of the lung following surgical operations.

Physical Signs. A lobule, lobe or entire lung may be involved and occasionally the condition is bilateral. The lung area may alternate in collapse and expansion over a period of a week before clearing up entirely. The right lung appears to be involved three times more frequently than the left.

The examination of the chest shows diminution of, or even absent respiratory movements over the affected lung. The chest wall over the massive atelectasis presents a flattened appearance. The intercostal spaces are narrowed and depressed. The percussion note over the collapsed lung may be dull, due to the lack of air in the lung. This is usually posterior, occasionally it may be anterior. The part of the thoracic cavity not occupied by lung tissue due to collapse may be tympanitic, though more frequently it is hyperresonant. If the collapse is on the right side, the high position of the diaphragm with the upward displacement of the liver is most striking. Collapse of the right lung with the high diaphragm and liver flatness may be incorrectly diagnosed as a pleural effusion. Vocal fremitus is usually diminished or absent; rarely it is increased.

The quality of the breath sounds varies greatly. They are more often suppressed though occasionally are distinctly bronchial. Vocal resonance is absent or diminished over the collapsed lung in the cases with diminished breath sounds. Increased vocal resonance with bronchial breathing is present in the less frequent number of

cases. Over the thoracic cavity unoccupied by lung tissue, the breath sounds and vocal resonance are greatly diminished or absent. Râles, if present, are noted early in the condition or later as the collapse subsides. The râles are more likely to be coarse and of the musical type.

The unaffected lung usually presents an increased range of respiratory movements and a hyperresonant percussion note with exaggerated breath sounds. Large râles may be heard over this lung.

Displacement of the heart and mediastinum toward the affected side is usually the deciding factor in making the diagnosis. Without the displacement of the heart, the condition cannot be diagnosed with certainty by physical examination alone. In pulmonary atelectasis involving lobules of the lung, at times it is necessary to verify the clinical findings by Roentgen ray examinations.

The difference in the physical sign in the lungs is due to the degree of patency of the bronchi and the part of bronchial tree involved. When considerable air enters the bronchi, there is an increase in the intensity of the breath sounds and they are tubular in quality and in character. The signs with dullness suggest pneumonic consolidation.

The Roentgen ray is valuable in confirming physical findings especially in doubtful cases. The displacement of the heart toward the affected side is diagnostic.

Diagnosis. The diagnosis is made on the history of a nontoxic pulmonary condition sudden in onset, accompanied by cyanosis, cough, an increased respiratory rate, fever, increased pulse rate and the physical signs as described. The presence of a displaced heart and mediastinum toward the affected side with elevation of the dome of the diaphragm, verified by Roentgen ray examination, confirms the diagnosis of collapse of the lung.

Differential Diagnosis. The condition must be differentiated from pleurisy, with or without effusion, pneumothorax, pneumonia, pulmonary infarct or thrombosis, diaphragmatic hernia and acute dilatation of heart. Because the signs in collapse of the lungs closely simulate pneumonia, doubtlessly many cases of collapse are erroneously so diagnosed. The differential diagnosis from conditions resembling it is made by recognizing that in acute massive collapse of the lung the chest is immobile on the affected side with retracted interspaces, the diaphragmatic and cardiac encroachment on the affected side are extreme and the general symptoms are invariably less severe than in other acute pulmonary conditions with equally extensive physical signs. The absence of the toxic symptoms in collapse of the lung is most striking when compared with pneumonic infection.

Prognosis. The prognosis is good and any unfavorable results are believed to be due to the condition with which collapse is associated and not to the collapse itself. The prognosis is less favorable if

FIG. 1.—Roentgen ray photograph showing massive atelectasis of right lung with heart and trachea displaced toward the right.

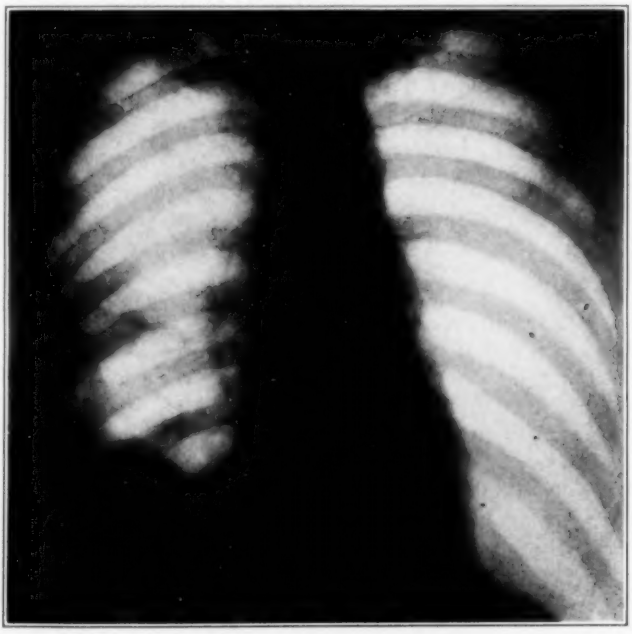

FIG. 2.—Clinical recovery made in three weeks, but Roentgen ray photograph shows slight degree of atelectasis present in the region of the fifth rib in the right mid-axillary line.

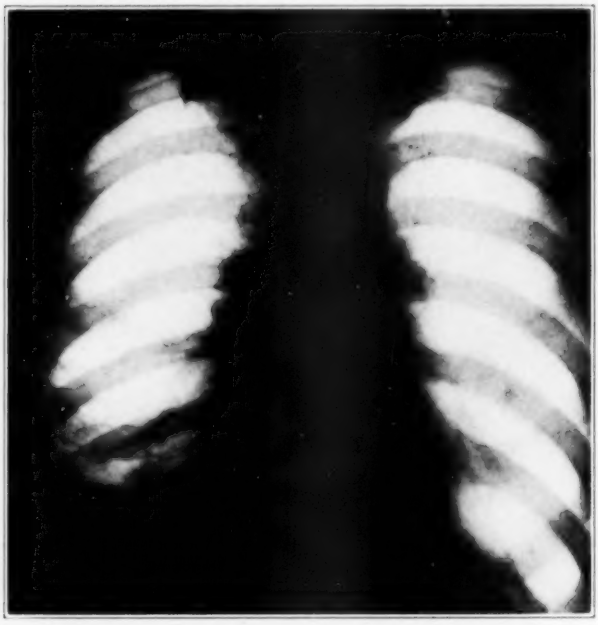

FIG. 3.—Roentgen ray photograph made eight weeks after collapse of right lung and three days prior to laparotomy. Lungs are normal. The heart and trachea are in normal position.

FIG. 4.—Roentgen ray photograph showing collapse of upper and middle lobe of right lung in case of lobar pneumonia. Although physical examination showed the right lung to be clearing the general condition grew worse due to failure of kidney function. The collapse of the lung occurred secondarily and thirteen days after the onset of pneumonia.

collapse is bilateral and persistent. These physical changes may furnish the soil for bronchopneumonia.

Case Reports. CASE I.—A man, aged fifty-one years, was admitted to the Jefferson Hospital March 14, 1926, suffering from epigastric pain after meals, nausea, vomiting and loss in weight. He had hematemesis ten years prior which was diagnosed, as due to ulcer of the duodenum. Since this attack he had been, on an ulcer diet, and free from symptoms. The past history otherwise discloses nothing worthy of note. His habits were very good. He did not suffer from respiratory infections. Generally his health was excellent until he suffered attacks of indigestion beginning in December, 1925, which gradually became worse and were accompanied by nausea and vomiting.

The physical examination on admission showed a well developed, symmetrical chest and expansion was equal. The percussion note over the lungs was resonant. No râles were present and the breath sounds were normal. The apex beat of the heart was visible in the fifth left interspace in the midclavicular line. The sounds occurred regularly and were well heard. No murmurs were present. The abdomen showed nothing worthy of note except slight epigastric tenderness.

Seven days after admission, on March 21, the patient, having vomited frequently, suddenly became cyanotic, developed cough and expectoration which was streaked with bright red blood and within six hours had a temperature of 101° F., a pulse of 92 and respirations of 30 per minute. Prior to this change he was not confined to bed. The right chest showed diminished expansion. There was dullness posteriorly over the apex of the right lung with bronchial breathing. A few coarse râles were noted. Anteriorly the percussion note was hyperresonant in the upper two-thirds of chest, breath sounds were distant and there were no râles. The lower third of right chest anteriorly and posteriorly gave a flat note. The apex of the heart was palpable in the fourth left interspace along the sternal border.

The leukocytes numbered 7800. Repeated examinations of the sputum were positive for blood and showed gram negative diplococci with a few pus cells. A diagnosis was made of collapse of the right lung. The patient continued to have a temperature ranging from 99° to 103° F. for a period of three weeks from onset. The pulse rate ranged from 70 to 122 per minute and the respirations from 20 to 48 per minute. The leukocyte count varied from 7800 to 17,200 and gradually returned to normal.

The Roentgen ray examination (Fig. 1) made March 29 showed a rather high degree of collapse of the right lung. The heart and trachea were displaced to the right. There was a small air-containing area in the right lower lobe, but the upper and middle lobes were entirely airless.

The patient made a clinical recovery in three weeks but the Roentgen ray (Fig. 2) examination at that time showed a slight degree of collapse present in the region of the fifth rib, mid-axillary line. The treatment was symptomatic, including codein in half-grain doses for cough.

The patient left the hospital and returned one month later for a surgical operation. Prior to operation a Roentgen ray examination (Fig. 3) showed the right lung to be normal. At operation the surgeon discovered an inoperable carcinoma of the stomach. The patient died six months later from the cancer of the stomach with metastasis to the liver. No further pulmonary symptoms developed.

The etiologic factors in the production of collapse were not evident. We believed that during the periods of vomiting he may have insufflated some of the vomitus which produced the obstruction and collapse.

During the violent paroxysms, he coughed up the insufflated material but the inflammatory reaction of the lung continued, gradually subsiding and the

lung returned to normal. There was no evidence of metastasis to account for lung symptoms.

The outstanding features during the collapse were the deep cyanosis which persisted for about one week, the blood spitting and the lack of any toxic symptoms, with a complete recovery from pulmonary symptoms with persisting gastric disturbances.

CASE II.—A man, aged fifty-five years, was admitted to the Jefferson Hospital April 4, 1927, with a history of having been ill for three days, beginning with a chill, fever, pain in right side, cough and blood spitting. The patient was mentally dulled, although able to be aroused sufficiently to answer questions. His past history was unimportant except that for twenty-five years he was a continuous user of whisky.

On physical examination, moderate cyanosis was present. Expansion was limited over the right chest. The percussion note was dull posteriorly over the right lung extending from the inferior angle of scapula to the liver. The breath sounds were distant and tubular in character. Occasionally râles were heard. The apex beat was palpated in the fifth left interspace midclavicular line. The sounds were well heard and there were no murmurs. The abdomen was tympanitic. The liver and spleen were not palpable.

The temperature was 101° F., the pulse rate 110 per minute and the respirations 32 per minute. The leukocyte count was 20,500. The urine showed a trace of albumin with many hyaline and granular casts.

The blood nonprotein nitrogen was 52.63 mg. per 100 cc. The sputum was positive for blood and pneumococci.

These findings suggested a lobar pneumonia involving the middle and lower lobes of the right lung.

On the second day in the hospital, the upper lobe of the right lung showed signs of consolidation, auricular fibrillation developed, and the patient's general condition was worse.

On April 10, six days after admission, his chest signs seemed to be clearing but his general condition did not seem to be greatly improved, due to his altered kidney function. A considerable quantity of tenacious sputum was being coughed up and caused the patient much distress.

On April 13, the physical signs of the patient changed: A tympanitic note was present over the right chest anteriorly over the upper and middle lobes. Below there was flatness. The signs on auscultation were also greatly altered. There was blowing breathing over the area of tympany. Over the flat area, neither râles nor breath sounds were heard. The heart was displaced toward the right.

Roentgen ray examination confirmed the physical findings and the clinical diagnosis of collapse of the right lung (Fig. 4).

The patient died on the fifteenth day of April from uremia. It was believed that the collapse was due to plugging of the bronchus with plugs of secretion.

Summary. 1. The occurrence of pulmonary atelectasis is reported in a case of pneumonia and in 1 of cancer of the stomach.

2. Pulmonary atelectasis occurs more frequently than is generally recognized in association with nonsurgical and nontraumatic cases.

3. It is a definite clinical entity and readily diagnosed by its physical signs and clinical course.

4. Until more conclusive evidence is presented, the mechanical obstruction theory as to etiology is the most plausible since removal of the obstruction has resulted in prompt expansion of the lung.

Experimentally the condition has been reproduced in animals by the injection into their bronchi of material removed from the bronchi of patients suffering from pulmonary atelectasis. The abolition of the cough reflex in dogs followed by the introduction of an acacia solution into their bronchi has produced pulmonary atelectasis which disappeared when the acacia solution was aspirated through the bronchoscope.

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THE VOLUME AND HEMOGLOBIN CONTENT OF THE RED BLOOD CORPUSCLE.

Simple Method of Calculation, Normal Findings, and Value of Such Calculations in the Anemias.

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The work of Price-Jones[1,2,3] has brought to the attention of the clinician the value of the determination of the size of red blood cells in the study of the blood. By the Price-Jones method, the diameter of the red cell is taken as a criterion of its size. It has been pointed out[4] that the thickness of red cells is as variable as their diameter, or even more so, and that the determination of actual cell volume is therefore preferable to the measurement of

cell diameter. Determination of the actual amount of hemoglobin in each cell is of value in gaining a clearer conception than has been afforded by the determination of the various indexes regarding the nature of various types of anemia.

It is possible from a knowledge of the red-cell count, hemoglobin content, and total cell volume of a given sample of blood, to calculate the average volume of the individual red blood cells contained therein, as well as their hemoglobin content. It is obvious that where the total cell volume per unit of blood and the total number of cells per unit of blood, are known, the average volume of each cell can be calculated by a simple process of division. The volume of the average red blood corpuscle in a given sample of blood, expressed in cubic microns (or 10^{-12} cc.), is determined by dividing the cell volume, expressed in cc. per 1000 cc. of blood, by the red-cell count, expressed in millions (and fraction thereof) per cubic millimeter of blood. To avoid confusion with total cell volume, it is suggested that the term "corpuscular volume" be used when referring to the volume of the individual red blood corpuscle. It is used hereafter with this meaning.

Similarly, where the amount of hemoglobin per unit of blood and the number of corpuscles per unit of blood, are known, the determination of the amount of hemoglobin in each corpuscle is easily made. This is concerned with the same properties as the well known "color index," but is differently expressed. The hemoglobin content, expressed in grams per 1000 cc., divided by the red-cell count, expressed in millions per cubic millimeter, gives the hemoglobin content of the average red cell in 10^{-12} gm. This will be referred to, hereafter, as "corpuscular hemoglobin."

The actual proportion of the substance of each red cell taken up by hemoglobin may be calculated by dividing the corpuscular hemoglobin by the corpuscular volume; or, directly, by dividing the hemoglobin content of a given sample of blood, expressed in grams per 100 cc., by the total cell volume expressed in cc. per 100 cc.

Illustration of Method of Calculation. A sample of blood is found to contain 5.85 million red cells per c.mm., 15.87 gm. of hemoglobin per 100 cc. (or 158.7 gm. per 1000 cc.), and 46.5 cc. of packed red cells per 100 cc. of blood (or 465 cc. per 1000 cc.). Then, the average corpuscular volume is $\frac{465}{5.85} = 79.5$ c.μ. (or 79.5×10^{-12} cc.); the average corpuscular hemoglobin is $\frac{158.7}{5.85} = 27.1 \times 10^{-12}$ gm.; proportion of hemoglobin in the average cell is $\frac{27.1}{79.5} \times 100 = 34.1$ per cent (or $\frac{15.87}{46.5} \times 100 = 34.1$ per cent).

For calculations such as have been described to be of any value, it is of course first essential that accurate methods be used in deter-

mining cell count, hemoglobin content and cell volume. The accurate determination of hemoglobin content is a difficult problem. For the research worker the very accurate method of determining the oxygen capacity of blood (van Slyke[5]) is available, but the various clinical hemoglobinometers have been shown to be inaccurate.[6,7] The writer[8] has found that the Newcomer instrument, although inaccurate as obtained from the manufacturer, is consistent in its error when compared with readings by the van Slyke apparatus, so that a correction curve can be plotted. Readings by the Sahli instrument are higher than those determined by the van Slyke method. The error, although not as consistent in degree as is that of the Newcomer instrument, is sufficiently regular to render the instrument of some value when a correction is made.

Accurate determinations of cell volume can be made by centrifuging a quantity of blood in a carefully calibrated tube. It is important, however, that due allowance be made for any change in the normal osmotic pressure of the blood and consequent effect on total cell volume resulting from the method used in collecting the blood. Thus it has been found[8] that the addition of 20 mg. of solid neutral potassium oxalate to 10 cc. of blood results in a decrease of cell volume of 3.68 per cent, while the addition of 40 mg. to 10 cc. of blood causes a shrinkage of 6.7 per cent.

The Volume of the Normal Red Blood Corpuscle. Starling,[9] as the result of the measurement of models of high magnification, gives the volume of the normal red blood cell as being 0.0000000722 c.mm. (or 72.2 c.μ.). Wintrobe and Miller[8] report elsewhere cell counts, hemoglobin and cell volume determinations in 100 healthy young men residing in the South. In Table I are found the calculated corpuscular volume and hemoglobin of each of these bloods. The average corpuscular volume was 79.8 c.μ. Fig. 1 shows that 80 per cent ranged between 70 and 87 c.μ.

TABLE I.—ABSOLUTE CELL DETERMINATIONS IN ONE HUNDRED NORMAL YOUNG MEN.

Subject.	Age.	Red cell count, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Corpuscular volume, c.μ.	Corpuscular hemoglobin, 10^{-12} gm.	Proportion of hemoglobin in cell.
1	19	5.48	13.40	83.8	24.5	29.2
2	24	5.69	14.50	59.9	25.5	42.5
3	22	5.59	15.25	74.1	27.3	36.8
4	24	6.61	16.20	75.2	24.5	32.5
5	21	6.09	16.05	82.3	26.4	32.0
6	22	5.54	16.60	86.5	29.9	34.6
7	23	6.03	16.20	79.0	26.9	34.1
8	27	5.20	16.20	90.2	31.2	34.7
9	27	4.68	15.93	85.9	34.0	39.6
10	28	5.88	16.05	78.0	27.3	35.0
11	23	5.40	16.75	89.5	31.0	34.7
12	22	5.53	18.30	84.3	32.9	39.1
13	22	5.32	16.75	96.8	31.5	32.4
14	24	4.70	16.33	78.3	34.7	44.3

TABLE I.—ABSOLUTE CELL DETERMINATIONS IN ONE HUNDRED NORMAL YOUNG MEN.—*Continued.*

Subject.	Age.	Red cell count, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Corpuscular volume, c.μ.	Corpuscular hemoglobin, 10^{-12} gm.	Proportion of hemoglobin in cell.
15	22	5.84	17.02	68.9	29.1	42.2
16	24	5.32	16.90	85.2	31.8	37.3
17	21	5.37	16.05	72.5	29.9	41.3
18	20	5.58	17.25	78.0	30.9	39.6
19	25	6.53	17.25	73.7	26.4	35.8
20	25	5.14	15.65	84.3	30.4	36.1
21	23	5.64	14.80	85.0	26.1	30.7
22	21	5.62	16.00	81.8	28.5	34.8
23	22	5.99	15.95	63.3	26.6	42.0
24	25	6.15	16.60	76.8	27.0	35.0
25	21	6.67	16.35	64.7	24.5	37.9
26	21	5.46	16.25	90.0	29.8	33.2
27	23	5.27	15.80	93.0	30.0	32.2
28	23	4.98	16.05	94.5	32.2	33.8
29	23	5.18	15.24	97.5	29.4	30.2
30	21	6.69	16.20	70.0	24.2	34.6
31	21	5.58	16.05	83.0	28.8	34.7
32	24	6.71	17.50	84.3	26.1	31.0
33	26	5.80	15.23	78.5	26.3	33.5
34	24	5.71	15.38	79.6	26.9	33.8
35	25	5.24	15.77	78.4	30.1	38.4
36	28	5.45	16.66	89.6	30.6	34.2
37	24	5.57	16.95	82.7	30.4	36.8
38	24	5.75	16.27	75.0	28.3	37.7
39	24	5.52	15.25	85.8	27.6	32.2
40	25	6.12	16.48	77.3	26.9	34.8
41	22	5.86	16.25	80.8	27.7	34.2
42	24	6.21	15.93	70.2	25.7	36.7
43	21	5.30	15.45	88.1	29.2	33.2
44	22	5.97	15.48	81.4	25.9	31.8
45	23	5.55	16.00	81.0	28.8	35.6
46	22	6.33	15.93	81.4	25.2	31.0
47	23	6.23	16.75	78.2	26.9	34.4
48	25	6.41	16.00	77.7	26.1	33.6
49	23	5.94	16.40	80.0	27.6	34.7
50	23	5.74	15.94	68.9	27.8	40.4
51	23	7.35	17.85	74.0	24.3	33.0
52	23	6.57	16.70	73.7	25.4	34.7
53	21	6.19	16.55	84.4	26.7	31.7
54	23	7.53	15.70	62.7	20.9	33.6
55	25	6.64	16.00	73.5	24.1	33.0
56	25	6.88	17.35	71.7	25.2	35.2
57	25	6.61	16.10	79.9	24.4	30.6
58	24	6.35	16.10	79.6	25.4	31.9
59	23	6.36	15.80	71.4	24.8	34.8
60	24	6.46	17.60	80.3	27.2	34.1
61	25	5.09	14.50	81.6	28.5	34.9
62	27	6.29	17.50	70.5	27.8	39.4
63	26	6.24	14.80	73.0	23.7	32.5
64	23	4.82	14.30	83.6	29.7	35.5
65	22	5.35	15.60	83.8	29.2	34.8
66	23	5.87	15.22	71.8	25.9	36.0
67	30	6.24	16.60	82.4	26.6	32.2
68	25	5.58	15.50	86.5	27.8	32.2
69	21	4.94	15.40	95.0	31.2	32.8
70	22	6.18	16.05	81.6	26.0	31.8
71	22	6.34	16.05	82.9	25.3	30.6
72	22	6.13	15.50	68.5	25.3	37.0

TABLE I.—ABSOLUTE CELL DETERMINATIONS IN ONE HUNDRED NORMAL YOUNG MEN.—*Continued.*

Subject.	Age.	Red cell count, millions per c.mm.	Hemoglobin, gm. per 100 cc.	Corpuscular volume, c.μ.	Corpuscular hemoglobin, 12^{-12} gm.	Proportion of hemoglobin in cell.
73	21	5.55	15.65	86.4	28.2	32.7
74	21	5.44	15.85	84.5	29.1	34.4
75	21	5.86	16.20	83.3	27.6	33.1
76	28	5.67	14.30	74.1	25.3	34.1
77	27	5.86	13.70	80.6	23.4	29.0
78	24	5.38	13.75	85.1	25.6	30.1
79	24	6.21	14.30	74.1	23.0	31.0
80	21	5.78	14.35	81.8	24.8	30.3
81	21	6.31	15.65	81.1	24.8	30.6
82	25	5.89	16.20	82.1	27.5	33.5
83	24	6.11	16.20	80.8	26.5	32.8
84	23	6.89	16.42	71.5	23.8	33.3
85	30	5.96	16.28	81.7	27.3	33.4
86	24	6.00	16.38	83.7	27.3	32.6
87	22	6.79	16.75	74.0	24.7	33.4
88	28	5.17	14.20	80.2	27.5	34.3
89	25	5.57	15.85	82.4	28.5	34.5
90	30	5.39	16.42	93.4	30.5	32.7
91	21	5.90	15.18	69.6	25.7	36.9
92	23	6.60	17.00	77.3	25.8	33.3
93	27	5.78	15.80	84.1	27.2	32.3
94	24	5.13	14.30	83.0	27.9	32.4
95	25	5.61	15.30	76.5	27.3	35.7
96	29	6.44	15.24	71.7	23.7	33.1
97	26	5.34	14.65	76.6	27.4	35.8
98	29	5.68	14.45	75.6	25.4	33.6
99	21	5.61	14.36	83.4	25.6	30.7
100	28	5.01	14.30	88.5	28.5	32.2
Average		5.85	15.87	79.8	27.3	34.4

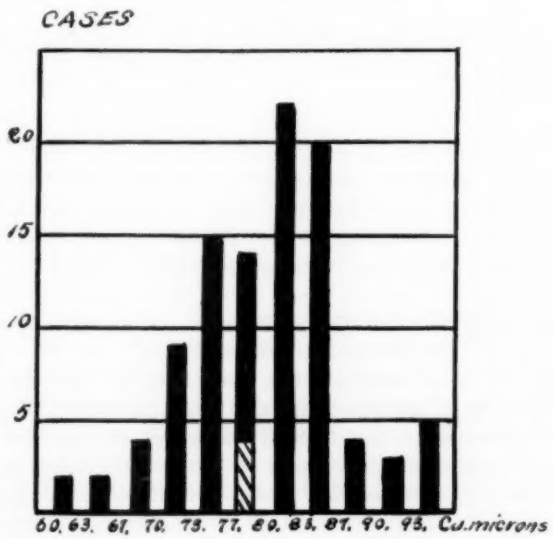

FIG. 1.—Volume of average red blood cell in one hundred healthy young men.

In Table II are found the average, maximum and minimum corpuscular volumes as calculated from the available reliable data for normal young men between nineteen and thirty years of age.

TABLE II.—VOLUME OF RED BLOOD CORPUSCLES IN HEALTHY YOUNG MEN (EXPRESSED IN C.μ.).

Author.	No. of men.	Average.	Maximum.	Minimum.
Osgood[7] (Oregon)	94	86.1	95.5	71.3
Haden[10] (Kansas City)	20	91.9	97.0	87.0
Gram and Norgaard[11] (Denmark)	7	85.2	88.7	82.9
Bie and Möller[12] (Denmark)	10	83.9	90.0	76.7
Wintrobe and Miller[8] (Louisiana)	100	79.8	97.5	59.9
Averages		83.8	95.6	68.3

The average corpuscular volume in the South appears to be definitely lower than that calculated for other parts of the world. This may be due to a difference in technique or be the effect of climate. The very high and the very low figures recorded are probably the result of technical error. Our lowest figure (59.9) was partially due to the occurrence of some hemolysis in the centrifugated specimen.

The average corpuscular volume as calculated from reliable data for the blood of healthy young women between eighteen and thirty years of age, is as follows:

TABLE III.—AVERAGE CORPUSCULAR VOLUME IN HEALTHY YOUNG WOMEN.

Author.	No. of women.	Average volume, c.μ.
Osgood[13]	100	88.5
Haden[10]	9	92.8
Gram and Norgaard[11]	6	88.0
Bie and Möller[12]	10	81.7
Total	125	88.2

The average figure for young women is somewhat higher than that for men of the same age, probably largely on account of the fact that figures for women in the South are not available. In 115 of the above cases, the corpuscular volume ranged from 98.1 to 76.5 c.μ.

Accurate statistics for the calculation of normal corpuscular volume in other age groups are not available.

Attempts made to ascertain the possibility of the identification of different races of mankind through the application of micrometry[14] failed because of the normal variation in the size of cells. Price-Jones[15] considers that there is a diurnal variation in size. The variation in corpuscular volume indicated by the figures enumerated above, aside from the extremes resulting from technical error, is, therefore, probably a true manifestation of the normal.

As between the two sexes, there appears to be only a slight difference in size, the cells of females being slightly larger. The normal range in size of red cells for young adults of both sexes may, therefore, probably be taken as being between 70 and 98 c.μ. with the great majority occurring well within these figures.

It is interesting to compare these normal figures with findings in various conditions of anemia. Haden[10] found an average corpuscular volume of 128 c.μ in 20 cases of pernicious anemia. The lowest figure was 108 c.μ (a case in the stage of remission), while the highest was 163 c.μ. Again, in 26 cases of hemolytic secondary anemia of various types, the corpuscular volume ranged from 63 to 97 c.μ. In 8 cases of hemorrhagic secondary anemia the cells ranged from 62 to 74 c.μ in size with an average of 71 c.μ.

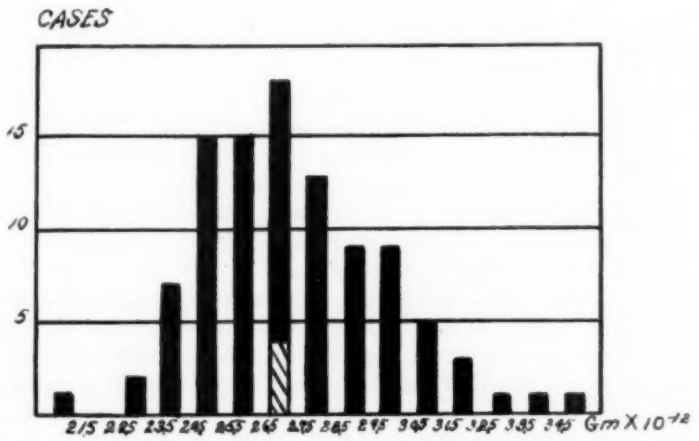

FIG. 2.—Grams of hemoglobin in average cell in one hundred healthy young men.

Haden points out that a relatively small increase in the diameter causes a relatively great increase in its volume. An increase in diameter of 1 μ causes an increase in cell volume of approximately 44 per cent. It seems to me that much of the valuable information obtained by measuring the diameter of red cells in pernicious anemia can be more easily gained by the simple calculations described above. There is the theoretical objection that where there are many microcytes as well as macrocytes (that is, the Price-Jones curve has a broad base) the increase in corpuscular volume may be obscured by the calculation of an *average* corpuscular volume. Practically, however, there are usually enough macrocytes present to produce a noticeable increase in the average corpuscular volume; that is, the Price-Jones curve is definitely swung to the right. In pernicious anemia, just as the volume index is always above 1, so the corpuscular volume is always greater than normal.

Hemoglobin Content of the Normal Red Blood Corpuscle. In Table IV are found average, maximum and minimum corpuscular hemoglobin as calculated from the data supplied by various authors for normal young men between the ages of nineteen and thirty years. Frequency Fig. 2 shows that 91 per cent of the men examined by Wintrobe and Miller had cells containing an average of 23.5 to 31.5 x 10^{-12} gm. of hemoglobin.

TABLE IV.—HEMOGLOBIN CONTENT OF RED CELLS IN HEALTHY YOUNG MEN (EXPRESSED IN 10^{-12} GM.).

Author.	No. of men.	Average.	Maximum.	Minimum.
Osgood[7] (Oregon)	137	29.2	35.7	24.6
Haden[10] (Kansas City)	20	31.1	33.4	29.2
Gram and Norgaard[11] (Denmark)	7	27.6	28.2	27.3
Bie and Möller[12] (Denmark)	10	26.7	28.8	25.4
Wintrobe and Miller[8] (Louisiana)	100	27.3	34.7	23.0
Averages		28.7	34.7	24.5

For normal young women between eighteen and thirty years of age, calculated corpuscular hemoglobin is as follows:

Osgood,[13] 100 women, averaging 28.5 x 10^{-12} gm.
Haden,[10] 9 women, averaging 31.3 x 10^{-12} gm.
Gram and Norgaard,[11] 6 women, averaging 27.9 x 10^{-12} gm.
Bie and Möller,[12] 10 women, averaging 28.1 x 10^{-12} gm.
Total, 125 women, averaging 28.6 x 10^{-12} gm.

In 115 of these individuals, the highest corpuscular hemoglobin was 33.8 x 10^{-12} gm., while the lowest figure was 23.7 x 10^{-12} gm.

From these calculations it appears, therefore, that the red blood corpuscles of the blood of healthy young adults contain an average of 28.7 x 10^{-12} gm. of hemoglobin and that the normal range occurs between approximately 24 and 33 x 10^{-12} gm.

In Table V, the actual proportion of hemoglobin contained in normal red blood cells, as calculated from the data of the various authors quoted, is indicated. Fig. 3 shows that in 84 per cent of the men examined by Wintrobe and Miller hemoglobin content of the average cell ranged from 30 to 37 per cent.

TABLE V.—PROPORTION OF HEMOGLOBIN IN NORMAL RED BLOOD CELLS.

Author.	No. of men.	Average.	Maximum.	Minimum.
Osgood[7] (Oregon)	94	33.1	43.8	30.4
Haden[10] (Kansas City)	20	33.9	36.2	32.2
Gram and Norgaard[11] (Denmark)	7	32.4	33.7	30.8
Bie and Möller[12] (Denmark)	10	31.8	33.1	29.4
Wintrobe and Miller[8] (Louisiana)	100	24.4	44.3	29.0
Averages		33.7	42.6	29.9

The corresponding figures for women of the same age are:

Osgood,[13] 100 women, averaging 32.2 per cent.

Haden,[10] 9 women, averaging 33.7 per cent.
Gram and Norgaard,[11] 6 women, averaging 31.7 per cent.
Bie and Möller,[12] 10 women, averaging 34.4 per cent.
Total, 125 women, averaging 32.5 per cent.

The highest proportion of hemoglobin in 115 of these women was 37.2 per cent, while the lowest figure was 28.1 per cent.

The average for the two sexes is 33.3 per cent. A slightly lower percentage of hemoglobin appears to be present in the cells of women than in those of men of the same age. The great majority of the figures range between 30 and 40 per cent. This is in fair agreement with the stated composition of healthy red blood cells, namely: water, 56.5 parts; absolute hemoglobin, 41.1 parts; other proteids, fats, and so forth, 2 to 4 parts.[16]

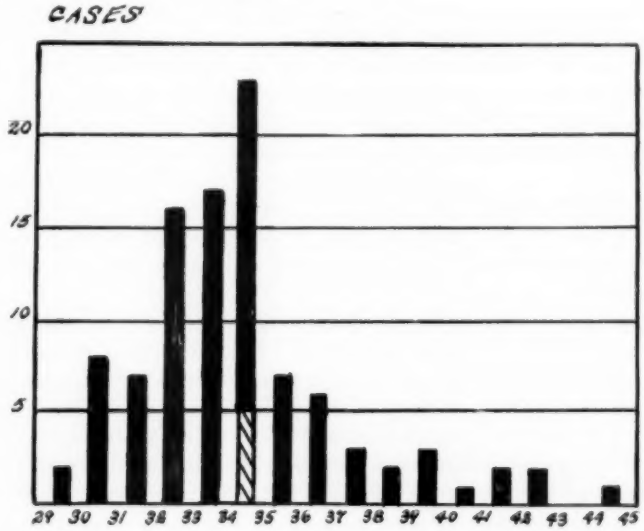

FIG. 3.—Percentage of hemoglobin in average red cell in one hundred healthy young men.

Determination of the absolute hemoglobin content of cells is of particular interest in the consideration of pernicious anemia. In this disease, the characteristic change is an increase in the volume of the red blood cells. These cells, however, are not supersaturated with hemoglobin, as is commonly supposed. They frequently do contain more hemoglobin than is found in normal cells, but this increase is never as great as the increase in the volume of the cell. Thus Haden[10] found in 20 cases of pernicious anemia that the cells contained from 21.1 to 46.8 x 10^{-12} gm. of hemoglobin with an average of 37.5 x 10^{-12} gm. The actual percentage of hemoglobin in these cells, however, ranged from 16 per cent to 34.9 per cent and in not 1 case did it exceed the normal limit. Likewise, the saturation index never rose above 1.

The Relation between Absolute Cell Determinations and the Indexes. The relationship between absolute cell determinations and the three indexes is probably best illustrated graphically:

$$\frac{\text{Vol. (cc. per 1000 cc.)}}{\text{R.B.C. (in millions)}} = \text{corpuscular volume in c.}\mu \qquad \frac{\text{Vol., per cent}}{\text{R.B.C., per cent}} = \text{volume index.}$$

$$\frac{\text{Hb. (gm. per 1000 cc.)}}{\text{R.B.C. (in millions)}} = \text{corpuscular hemoglobin in } 10^{-12} \text{ gm.} \qquad \frac{\text{Hb., per cent}}{\text{R.B.C., per cent}} = \text{color index.}$$

$$\frac{\text{Hb. (gm. per 100 cc.)}}{\text{Vol. (cc. per 100 cc.)}} = \text{proportion of hb. in cell;} \qquad \frac{\text{Hb., per cent}}{\text{Vol., per cent.}} = \text{saturation index.}$$

From the above, it can be seen that corpuscular volume and volume index express the same relationship with the difference that the latter is an expression of the volume of the average cell in proportion to the normal volume and red-cell count. Similarly, both corpuscular hemoglobin and color index refer to the actual amount of hemoglobin in the average cell, with the difference that color index expresses that amount *in proportion to the normal*—a "normal" which, by the way, has, heretofore at least, been based on inaccurate and unreliable data. The last formula shown above expresses the actual proportion of the substance of each cell taken up by hemoglobin, the saturation index expressing this proportion in terms of normal.

These simple methods of making absolute cell determinations are not offered to replace the indexes. It is believed, however, that such calculations do afford a clearer conception of the details of size and hemoglobin content of red cells, as well as a better understanding of the meaning of the indexes. Furthermore, the accurate determination of the indexes presupposes a knowledge of the true normal. As long as our generally accepted figures for normal—particularly normal hemoglobin content of blood—are as varied and inaccurate as they now are, absolute cell determinations have a particular value.

Summary. 1. Simple methods for the calculation of the volume of the individual red blood corpuscle, as well as its hemoglobin content, are described.

2. The terms, "corpuscular volume," and "corpuscular hemoglobin" are defined, and the normal corpuscular volume and corpuscular hemoglobin, as calculated from accurate data supplied by various authors, are given.

3. The value of absolute cell determinations in the anemias is briefly discussed and their relationship to the indexes indicated.

Conclusions. The red blood corpuscles of the blood of healthy young adults vary between 70 and 98 c.μ in size, with the majority well within these figures. The average cell contains 28.7×10^{-12} gm. of hemoglobin, the latter constituent taking up, on the average, 33.3 per cent of the entire substance of the cell.

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BLOOD SEDIMENTATION TEST COMBINED WITH A SERUM REACTION IN THE DIAGNOSIS AND PROGNOSIS OF TUBERCULOSIS.

A Preliminary Study of One Hundred and Forty-seven Cases.

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Variations in the rate of sedimentation of blood cells in healthy and diseased individuals, phenomena noted by ancient observers, have given rise to a considerable amount of recent experimentation. The work of Fahreus in 1918 and, more recently, of Westergreen

and others has served to put the test on a stronger foundation, and it can now be definitely stated that a distinct and more or less constant correlation has been established between erythrocyte suspension stability and quantitative tissue destruction processes in the human body. The reaction is, however, nonspecific and gives parallel results in pelvic inflammatory disease, acute infections, tuberculosis, and so forth. It is only when the disease condition is definitely identified or when all but one of the conditions known to produce the sedimentation phenomena are ruled out that it can be used as an accurate measure of pathologic activity attributable to that disease. It has seemed to be of considerable value as an aid in determining the *status præsens* and estimating the prognosis in tuberculosis, but, here again, one of its chief limitations has been its nonspecificity.

It is to attempt to overcome this factor that, in conducting the investigation detailed in this report, the blood sedimentation test has been performed in conjunction with a serum test which has for its object the determination of the presence or absence of active tuberculosis. The serum test employed here is one which depends for its positive result upon precipitin phenomena occurring in the presence of tuberculous precipitin and possibly other specific antibodies in the patient's serum. The reaction is, therefore, intended merely as a means for ascertaining the presence and approximate combining power of tuberculous antibodies in the blood serum of a given patient. It involves the use of a water-soluble extract of tubercle bacilli prepared by Eli Lilly & Co., and marketed under the trade name "Tubercumet." The suspension stability test which has been used here is essentially that employed by Jacob Cutler and described as his "finger-puncture method;" however, we have used blood obtained by venipuncture, another portion of the same specimen being used for the serum reaction. A brief description of the technique follows:

Technique. Under aseptic conditions, about 5 cc. of blood is obtained by puncture of an arm vein. It is best to secure this blood at least two hours after the patient's last meal, in order to have it as free from fats as possible; these are said to interfere with the precipitin reaction: 1.8 cc. of the blood is placed in a test tube containing 0.2 cc. of a 3 per cent solution of sodium citrate, and thoroughly mixed; this prevents clotting in the specimen used for the sedimentation test. The remainder of the whole blood is allowed to clot, the cloth and cells separated by centrifugalization and the clear serum drawn off; this serum is refrigerated for twenty-four hours before use in the precipitin test.

Sedimentation Test. The citrated blood, thoroughly shaken and mixed to assure absence of clotting and good suspension of cells, is drawn up in a special pipette calibrated in cubic millimeters, to form a solid column of 40 c.mm. This pipette is the type used by

Cutler in his finger-puncture method. The time is noted, and readings of the height of the column of sedimenting cells are taken at five-minute intervals for one hour; these readings are recorded and embodied in a graph, the abscissæ of which represent the height of the cell column and the verticals of which are the five-minute time intervals. The curve so obtained is a graphic representation of the amount, rate and changes of rate of sedimentation, and may be classified in one of four arbitrarily constructed types:

1. Horizontal Line (Hor. L.), in which sedimentation is not complete within one hour, and amount of sedimentation is within normal limits. In adopting standards of normal limits, use has been made of the results reported by Greisheimer and by Cutler, and of the 16 normal cases of our group. The limit of amount of sedimentation is here considered as 9 mm. per first hour for males, 11 mm. for females.

2. Diagonal Line (Diag. L.), in which sedimentation is not complete within one hour, but amount is beyond normal limits.

3. Diagonal Curve (Diag. C.), in which sedimentation is complete within one hour, and the amount is less than 20 mm. at the end of the first fifteen minutes.

4. Vertical Curve (Vert. C.), in which sedimentation is complete within one hour and the amount is 20 mm. or more at the end of the first fifteen minutes.

Serum Test. One-fifth cubic centimeter of clear serum which has been refrigerated twenty-four hours is carefully overlaid in a small test tube (5 mm. diameter) with an equal amount of the water-soluble extract of tubercle bacilli, "Tubercumet." The entire test is performed under sterile conditions. The tube is examined for a ring at the interface of the two substances immediately and again at half-hour intervals for two hours, during which time it is kept in an incubator at 37° C. Following this, the tube is allowed to stand at room temperature for twenty-four hours and a sixth reading taken. The presence of a hazy, indefinitely marginated ring of almost immediate formation may be disregarded, as it is probably due to a fat reaction; such a ring is further identified by its remaining unchanged at the interface through the twenty-four-hour period. The true "Tubercumet" ring is a clearly defined one which forms more slowly, may continue to broaden during the two hours of incubation and either disappears after twenty-four hours or has moved to the upper surface of the extract, from which it clouds downward on gentle agitation. The width and definition of the ring are said to be proportional to the quantity of precipitin antibody in the patient's serum. The ring varies from 0.5 to 5 mm. in diameter and may be classified as:

Slight	(SR)	0 to 1 mm.
Moderate	(MR)	1 to 3 mm.
Heavy	(HR)	3 to 5 mm.

Interpretation of Findings. In a general way, most observers agree that the amount and rapidity of sedimentation are proportionate or, at least, parallel to the amount and rapidity of pathologic activity and tissue destruction. The curve obtained here represents this amount and rapidity graphically. If we assume it to be a fair measure of pathologic activity, the sharper the declivity of the curve, the greater the amount and speed of tissue destructive processes in the individual from whom the blood was obtained. The "Tubercumet" test, essentially a ring reaction, depends for its positive result upon the presence of tuberculous precipitin in the patient's serum. This antibody, it is then to be expected, should be found in:

1. The blood of tuberculous patients in some degree of direct proportion to their resistance to the pathologic process.

2. Some patients with healed lesions where antibodies are still present in the tissues. Negative precipitin reaction, conversely, should indicate the absence of antibody substances, and might be found in:

(*a*) The absence of tuberculous infection.

(*b*) Early cases in which antibodies have not yet developed.

(*c*) Far-advanced cases in which almost all resistance is broken and the body has almost ceased to produce precipitins.

(*d*) Old lesions where the need for their continued production has ceased.

Each of the tests may terminate, depending upon extent and rapidity of reaction, in one of four arbitrarily constructed types. They give us, theoretically at least, a means of estimating, in one case, something of the general tissue destruction occurring in the body and, in the other, something of the presence and strength of the individual's specific reaction to tuberculosis. It is evident that where the two tests are performed upon the same individual (here, upon portions of the same specimen of blood), there are sixteen possible combinations of the types of end result: Horizontal line sedimentation with negative serum reaction, diagonal line sedimentation with negative serum reaction, and so forth. If we assume each of the tests to be performing, with some efficiency and reliability its particular function, the following interpretation of results is logically suggested in Table I.

Analysis of Cases. A total of 147 individuals was used for this series of tests, divided into groups as follows: Normals, observation cases, incipient cases, moderately advanced and far-advanced cases. The latter two groups were further divided into A, B and C types.

1. Normal Individuals. Of our normal group, 7 were male and 9 female. All of these 16 showed negative precipitin reactions. The sedimentation of our males varied 1.5 to 9 mm., only 1 going below 5 during the hour. Among the females the sedimentations

varied from 1.5 to 10.5 mm., these results being a little higher than those obtained by most observers.

TABLE I.—SEDIMENTATION TESTS AND TUBERCUMET REACTION.

	SEDIMENTATION.			
	Horizontal L.	Diagonal L.	Diagonal C.	Vertical C.
Tuberculumet NEG.	1. No tuberculosis 2. Arrested tuberculosis; antibodies disappeared	1. No tuberculosis; some slight destructive disease 2. Apparently arrested tuberculosis	1. No tuberculosis; some destructive disease	1. No tuberculosis; some destructive disease. 2. Last stages of tuberculosis; a rapid decline and practically no resistance.
SR.	1. Incipient tuberculosis 2. Apparently arrested tuberculosis	1. Incipient tuberculosis 2. Improving tuberculosis 3. Very slowly progressive tuberculosis*	1. Tuberculosis plus some destructive disease 2. Tuberculosis; a poor resistance	1. Tuberculosis plus some destructive disease. 2. Tuberculosis; a rapid decline and practically no resistance.
MR.	1. Incipient tuberculosis 2. Improving tuberculosis 3. Apparently arrested tuberculosis	1. Incipient tuberculosis 2. Improving tuberculosis 3. Slowly progressive tuberculosis*	1. Tuberculosis plus some destructive disease 2. Tuberculosis; a fair resistance	1. Tuberculosis plus some destructive disease. 2. Tuberculosis; a poor resistance.
HR.	1. Incipient tuberculosis 2. Improving tuberculosis 3. Almost arrested tuberculosis	1. Improving tuberculosis 2. Tuberculosis; good resistance	1. Tuberculosis plus some destructive disease 2. Tuberculosis; fair resistance	1. Tuberculosis plus some destructive disease. 2. Extensive tuberculosis; a strong body reaction.

* For example, fibroid.

TABLE II.—OBSERVATION CASES.

Name.	Sex.	Race.	Age.	Sputum.	Wt.	Temp.	Complications.	Tubercumet.	Sedimentation.	
									Curve.	Amt., mm.
V. A.	M.	W	38	Neg.	Const.	Const.	Pneumonokoniosis	Neg.	Hor. L.	2.5
E. D.	F.	W	27	Neg.	Incr.	Sl.	.....	SR.	Not done	
M. O'R.	M.	W	45	Neg.	Const.	Norm.	Pneumonokoniosis	SR.	Diag. L.	14.0
A. L.	M.	W	39	Neg.	Incr.	Sl.	Empyema	SR.	Diag. C.	28.5
M. Z.	F.	W	20	Neg.	Const.	Sl.	Chronic nephritis, cold abscess, ischio rectal abscess, bone disease	SR.	Vert. C.	32.0

II. Observation Cases. The observation cases number 5, all of which have negative sputa and have never shown pulmonary involvement on physical examination. However, in only 1 of these was the Tubercumet test negative, and in this same one the sedimentation was within normal limits. The remaining 4 gave slight positive precipitin reactions and sedimentations varying from diagonal line to vertical curve. It is to be noted that each of these presented some complication of a more or less destructive nature, the least sedimentation occurring in a case with pneumo-

nokoniosis and emphysema, the next in a patient with pleural empyema, and the highest in a case complicated by various foci of destructive lesions. Actual pulmonary involvement may not have been sufficient for determination by physical diagnosis.

III. Incipient Cases. In this group of 9 patients it is notable that, while all offered sufficient history or symptomatology to be placed in a sanatorium as incipient cases of pulmonary tuberculosis, in 2 cases the precipitin tests were negative. Further investigation, however, shows that one of these has also a normal sedimentation and that there has always been grave doubt as to the diagnosis of tuberculosis; the other presents a diagonal line type of sedimentation curve and has by clinical signs only a healed lesion. The single case presenting a slight precipitin reaction occurred in an apparently very early case clinically. It is interesting to note that, of the three moderate precipitin reactions, the highest sedimentation, a diagonal curve, occurred in the one case which had had hemoptysis. The three heavy precipitin reactions, all showing horizontal line (normal) or diagonal line curves, would seem to indicate a high degree of antibody formation coupled with quite low-grade tissue destruction; in other words, a high resistance on the part of the patient's tissues.

IV. Moderately Advanced "A" Cases. The 8 negative Tubercumet reactions of this group occurred in a wide variety of cases. Of the 3 presenting normal sedimentation curves, 2 were apparently arrested cases, while the third was one in which the true condition was probably a cardiac one; the 3 cases with diagonal line sedimentation curves included 1 arrested, 1 healed and 1 of questionable tuberculosis with absence of pulmonary signs; the remaining 2 negative reactions were obtained in 2 rapidly declining patients who could no longer be included in the moderately advanced "A" cases.

Of the 7 slight positive reactions, 2 cases showed normal sedimentation charts; the 2 highest sedimentations, 1 diagonal line and 1 diagonal curve, occurred in the 2 patients who had had previous hemoptysis.

The three moderate reactions all occurred in patients presenting positive sputa and moderately high grades of sedimentation, all diagonal curves of 22 to 24 mm.

The six heavy Tubercumet reactions were all in patients having positive sputa and, with the exception of a single diagonal line of 18.5 mm., diagonal curve sedimentations; the 3 highest grades of sedimentation occurred in the three members of the group who were consistently showing loss of weight.

V. Moderately Advanced "B" Cases. Two of the three negative Tubercumet reactions in this group illustrate the conception that such a result is obtainable in a lesion where healing has occurred with resultant fibrosis and subsequent disappearance of the anti-

TABLE III.—INCIPIENT CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tuberculin.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
O. P.	F.	W	34	..	Gain	Norm.	Old pleurisy	Neg.	Hor. L.	6.0	Doubtful tuberculosis.
J. C.	F.	W	18	...	Gain	Norm.	.....	Neg.	Diag. L.	15.0	Healed lesion.
E. P.	F.	W	39	...	Gain	Norm.	Chronic bronchitis	Sl. pos.	Not done		
L. F.	M.	W	23	+5	Gain	Norm.	.....	Mod. pos.	Diag. L.	11.0	
A. F.	F.	W	39	...	Gain	Norm.	.....	Mod. pos.	Diag. L.	24.0	
J. D. M.	F.	W	21	...	Gain	Norm.	Hemoptysis	Mod. pos.	Diag. C.	26.5	
A. A.	M.	B	46	...	Gain	Sl.	.....	Heavy pos.	Hor. L.	4.5	
E. R.	M.	W	18	...	Gain	Norm.	.....	Heavy pos.	Hor. L.	9.0	
F. A.	F.	W	24	...	Gain	Norm.	.....	Heavy pos.	Diag. L.	23.0	

TABLE IV.—MODERATELY ADVANCED "A" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tuberculin.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
G. F.	M.	W	21	...	Gain	Norm.	Hemoptysis	Neg.	Hor. L.	1.0	Apparently arrested.
H. B.	M.	W	43	...	Gain	Norm.	.....	Neg.	Hor. L.	6.0	Apparently arrested.
C. F.	M.	W	21	...	Gain	Sl.	Hemoptysis	Neg.	Hor. L.	6.5	Cardiac disease.
A. M.	M.	W	32	...	Gain	Sl.	Gastric ulcer (?)	Neg.	Diag. L.	9.0	
F. N.	M.	W	37	...	Gain	Norm.	Pneumonokoniosis	Neg.	Diag. L.	13.0	Healed lesion.
J. P.	F.	W	26	..	Gain	Norm.	.....	Neg.	Diag. L.	14.0	Arrested.
J. G.	M.	W	20	+7	Loss	Sl.	.....	Neg.	Vert. C.	22.0	Rapid decline.
W. E.	M.	W	52	+2	Gain	Sl.	Bone	Neg.	Vert. C.	31.0	Rapid decline.
M. H.	F.	W	33	...	Gain	Sl.	.....	Sl. pos.	Hor. L.	7.0	
J. S.	M.	B	23	...	Gain	Norm.	.....	Sl. pos.	Hor. L.	9.0	
N. W.	F.	W	29	..	Gain	Sl.	.....	Sl. pos.	Diag. L.	10.0	
G. M. C. Q.	F.	W	33	..	Gain	Norm.	.....	Sl. pos.	Diag. L.	14.0	
W. S.	M.	B	31	+6	Gain	Sl.	Hemoptysis	Sl. pos.	Diag. L.	16.0	
C. T.	M.	W	23	+3	Gain	Sl.	Hemoptysis	Sl. pos.	Diag. C.	26.0	
E. W.	F.	W	21	...	Gain	Norm.	.....	Sl. pos.	Not done		
E. B.	F.	W	28	+5	Gain	Norm.	.....	Mod. pos.	Diag. C.	22.0	
W. J.	M.	B	31	+4	Gain	Sl.	Hemoptysis	Mod. pos.	Diag. C.	22.0	
R. F.	F.	W	16	+1	Gain	Norm.	.....	Mod. pos.	Diag. C.	24.0	
S. C.	M.	B	19	+5	Gain	Sl.	.....	Heavy pos.	Diag. L.	18.5	
M. B. A.	F.	W	22	+5	Loss	Sl.	Art. pneumothorax, hemoptysis	Heavy pos.	Diag. C.	27.5	
F. D.	M.	W	46	+5	Loss	Sl.	.....	Heavy pos.	Diag. C.	25.5	
W. K.	M.	W	25	+2	Loss	Sl.	Hemoptysis	Heavy pos.	Diag. C.	23.5	
A. K.	M.	W	24	+6	Gain	Norm.	.....	Heavy pos.	Diag. C.	21.5	
E. T.	F.	W	21	+2	Gain	Sl.	.....	Heavy pos.	Diag. C.	22.0	

TABLE V.—MODERATELY ADVANCED "B" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercumet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
J. S.	F.	W	27	...	Gain	Sl.	Cardiac hemoptysis	Neg.	Hor. L.	35.0	Apices fibroid.
E. S.	F.	W	33	...	Const.	Sl.	Tub. nephr.	Neg.	Hor. L.	6.5	Apices fibroid.
F. K.	F.	W	25	...	Const.	Sl.	.....	Neg.	Diag. C.	22.0	Bronchiectasis.
E. McK.	F.	W	19	+5	Loss	Sl.	.....	Sl. pos.	Diag. C.	24.5	
M. McC.	F.	W	43	+4	Const.	Sl.	.....	Sl. pos.	Vert. C.	30.0	
M. H.	F.	W	34	+5	Const.	Mod.	Scoliosis	Sl. pos.	Vert. C.	31.0	Bone.
S. K.	M.	W	40	+4	Const.	Sl.	.....	Mod. pos.	Diag. C.	20.0	
T. B.	M.	W	22	...	Gain	Sl.	Empyema (1)	Mod. pos.	Vert. C.	28.5	
							(2)	Heavy pos.	Diag. C.	26.0	
J. Z.	M.	W	18	+2	Gain	Sl.	.....	Heavy pos.	Diag. L.	23.0	
E. McC.	F.	W	20	+6	Gain	Norm.	.....	Heavy pos.	Diag. L.	24.0	
F. S.	F.	W	16	+5	Gain	Mod.	Hemoptysis	Heavy pos.	Diag. C.	22.0	
A. S.	F.	W	26	+8	Gain	Sl.	.....	Heavy pos.	Diag. C.	24.0	
C. T.	M.	W	47	...	Const.	Sl.	.....	Heavy pos.	Diag. C.	26.0	
N. I.	F.	W	17	+2	Gain	Mod.	.....	Heavy pos.	Diag. C.	28.0	

TABLE VI.—MODERATELY ADVANCED "C" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercumet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
M. W.	F.	W	16	...	Gain	Sl.	Bronchitis, mitral stenosis	Neg.	Hor. L.	4.0	Tuberculosis ?
D. K.	F.	W	33	+4	Gain	Sl.	.....	SR.	Diag. L.	23.0	Fibroid.
J. P.	M.	W	18	+2	Loss	Sl.	Hemoptysis	HR.	Diag. C.	22.5	
A. O.	F.	W	26	...	...	Sl.	Hemoptysis	HR.	Vert. C.	29.5	Pulmonary abscess.
T. S.	M.	W	60	...	Const.	Mod.	Bone tuberculosis, cold abscess	HR.	Vert. C.	30.0	
E. W.	F.	W	53	+7	Gain	Sl.	.....	HR.	Vert. C.	31.0	

bodies producing the reaction. The third negative occurred in a case diagnosed clinically as bronchiectasis and showing a diagonal curve type of sedimentation; sputum has always been negative.

The three slight positive Tubercumet reactions occurred in conjunction with either vertical or diagonal curve types of sedimentation and all in patients who were showing rather marked decline in their general condition.

The remainder of the positive reactions, moderate and heavy, reveal a generally high degree of sedimentation throughout; 2 diagonal line types are 23 and 24 mm. respectively, while the other 6 are of the diagonal curve type.

VI. Moderately Advanced "C" Cases. The single negative Tubercumet reaction in this class occurred in a patient who is in all probability nontuberculous; the physical signs are entirely those of mitral stenosis with secondary pulmonary congestion and chronic bronchitis; the sedimentation was entirely normal.

There was one slight positive Tubercumet reaction; this occurred in a patient with a chronic fibroid tuberculosis, whose sputum was positive once in 17 examinations and whose sedimentation was of the diagonal curve type.

There were no moderate reactions in this group and the heavy reactions occurred in a variety of conditions; 2 of these cases were those of advanced pulmonary tuberculosis; 1 was a case of bone disease and multiple cold abscess in which sputum had always been negative; the remaining one was a case in which the signs were wholly those of pulmonary abscess and sputum was consistently negative. In all these conditions sedimentation was of the diagonal or vertical curve type. We are unable to account for the heavy reaction, either in the case of E. W., where, clinically, the patient was rapidly declining, or the case of A. O., where apparently the lesion was not tuberculous in character.

VII. Far-advanced "A" Cases. The far-advanced "A" group includes 32 cases. The single negative Tubercumet showed a diagonal line sedimentation and was clinically an arrested case, but the time of the test was complicated by an abscess of the right hand.

Of the 4 slight positive reactions, 3 gave diagonal curves, all being clinically active cases and declining steadily. The fourth showed a vertical curve and was a case of Pott's disease and tuberculous kidney with a nephrectomy. There was very little lung involvement here, however; there were 3 continually draining sinuses from the back. Clinically, the case was going down hill, the slight reaction here indicating a gradual loss of body resistance to the disease.

Of the 10 cases with moderate reactions, 1 showed normal sedimentation. Clinically, this case was improving. However, the tests were favorable far out of proportion to clinical findings. Four of the 10 showed diagonal line sedimentations; of these cases, 3 had negative sputa. Of these, 1 was an arrested bone case,

TABLE VII.—FAR-ADVANCED "A" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tuberculinet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
A. McC.	M.	W	43	...	Const.	Norm.	.....	Neg.	Diag. L.	16.5	
J. C.	F.	W	46	+3	Gain	Sl.	.....	SR.	Diag. C.	25.0	
R. J.	M.	W	17	+6	Const.	Sl.	Hemoptysis	SR.	Diag. C.	26.0	Bone tuberculosis.
M. S.	M.	W	34	...	Gain	Sl.	Nephrectomy, Pott's disease	SR.	Vert. C.	27.5	Bone tuberculosis.
J. W.	M.	W	24	+5	Gain	Sl.	Hemoptysis	SR.	Diag. C.	23.0	
W. A.	M.	W	43	...	Const.	Norm.	Thick pleura	MR.	Diag. L.	10.0	
M. M.	M.	W	16	...	Gain	Sl.	.....	MR.	Diag. L.	17.0	
M. C.	F.	W	31	+4	Gain	Norm.	.....	MR.	Diag. L.	17.5	
M. M.	F.	W	23	...	Gain	Norm.	Tb. ankle, tb. larynx	MR.	Diag. L.	18.0	Bone tuberculosis.
J. R.	M.	W	39	+2	Gain	Norm.	Hemoptysis, nephritis	MR.	Diag. C.	22.0	
G. T.	M.	W	41	...	Const.	Sl.	Pneumonokoniosis, hemoptysis	MR.	Diag. C.	25.0	
D. E.	M.	W	23	+2	Gain	Sl.	Nephrolithiasis	MR.	Diag. C.	27.0	
G. A.	F.	W	23	+5	Gain	Norm.	.....	MR.	Diag. C.	28.0	
J. M.	M.	W	47	+6	Const.	Norm.	.....	MR.	Vert. C.	29.0	
J. H.	M.	W	28	+4	Gain	Norm.	.....	HR.	Hor. L.	7.5	
D. S.	M.	W	43	+5	Loss	Sl.	Syphilis, hemoptysis	HR.	Diag. L.	14.0	
Dr. L.	M.	W	58	+2	Const.	Norm.	.....	HR.	Diag. L.	21.0	
E. D.	M.	W	49	...	Const.	Norm.	Bronchiectasis	HR.	Diag. C.	19.0	
H. M.	M.	W	30	+5	Const.	Sl.	Ischiorectal abscess, syphilis	HR.	Diag. C.	21.0	
J. C.	M.	W	45	+4	Gain	Sl.	Pneumonokoniosis	HR.	Diag. C.	22.5	
E. R.	F.	W	22	+5	Const.	Sl.	.....	HR.	Diag. C.	23.0	
T. L.	M.	W	35	+4	Const.	Sl.	.....	HR.	Diag. C.	23.0	
T. F.	M.	W	41	+2	Loss	Sl.	Syphilis, emphysema pneumonokoniosis	HR.	Diag. C.	23.5	
M. H.	F.	W	32	+4	Const.	Sl.	.....	HR.	Diag. C.	24.0	
A. A.	M.	W	...	...	...	...	.....	HR.	Diag. C.	24.0	
V. K.	M.	W	37	+5	Loss	Sl.	.....	HR.	Diag. C.	25.0	
A. P.	F.	W	20	+2	Gain	Norm.	Hemoptysis	HR.	Diag. C.	25.0	
J. B.	M.	W	21	+6	Gain	Sl.	.....	HR.	Diag. C.	26.0	
H. G.	M.	W	29	+8	Gain	Norm.	.....	HR.	Vert. C.	27.0	
M. M.	F.	W	19	+5	Gain	Sl.	.....	HR.	Diag. C.	27.5	
A. S.	F.	W	25	+9	Gain	Sl.	.....	HR.	Diag. C.	31.0	

another a quiescent lung case and a third showed clinical improvement. The fourth, with a positive sputum, also showed clinical improvement. One case showed a vertical curve type of sedimentation; clinically, the disease was progressing over the patient's resistance.

Seventeen of the cases gave a heavy ring Tubercumet. The one with a horizontal line type was gaining weight, had normal temperature and apparently high resistance. Of the 2 with diagonal line sedimentation, 1 was improving and showed high resistance. However, the other was going down hill and clinically was contradictory to the favorable tests; there is a complication of syphilis, which may have vitiated the results. Of the 13 with diagonal curves, all show moderate activity in keeping with laboratory findings. The one showing a vertical curve has shown a clinical stability out of keeping with the sedimentation curve, although quite in keeping with the heavy resistance indicated by the Tubercumet.

VIII. Far-advanced "B" Cases. Of the 27 cases in the far-advanced "B" class, 2 presented negative Tubercumet reactions. One patient in the last stages of the disease shortly afterward had severe hemoptysis; his sedimentation showed a vertical curve type. The other, however, had a diagonal line sedimentation in spite of a rather down-hill clinical course of an unquestionable tuberculosis.

Two slight positive and 7 moderate positive Tubercumet reactions occurred in this group, all in conjunction with diagonal curve sedimentations of moderate degree. These were all definitely tuberculous cases with the disease well established and active.

Sixteen cases here showed heavy positive Tubercumet reactions with diagonal line sedimentations occurring in the 2 cases which, from a clinical standpoint, were improving. Of the remainder, 11 presented diagonal curve and 3 vertical curve types of sedimentation in some degree of accordance with the extent of the disease.

IX. Far-advanced "C" Cases. In the far-advanced "C" group there are 14 cases, all of which had positive sputa at some time, and involvement of three or more lobes. Of the 3 with negative Tubercumet reactions, 1 has shown a diagonal line sedimentation; this patient had a negative sputum for the year prior to the test and was doing fairly well clinically. The other 2 showed vertical curve sedimentations and clinically were rapidly going down hill.

Of the 3 with slight Tubercumets, 2 had empyema and were rapidly declining; the third had a vertical curve sedimentation in keeping with the clinical activity and loss of weight.

The two cases giving the moderate reaction died subsequent to the tests, following pulmonary hemorrhage.

Of the 6 cases showing heavy ring Tubercumets, 2 did not have blood sedimentations done. Two gave horizontal line types, but

TABLE VIII.—FAR-ADVANCED "B" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tubercumet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
G. C.	F.	W	35	+6	Loss	Sl.	Pleural effusion, art. pneumothorax	Neg.	Diag. L.	17.0	
H. O. S.	M.	B	37	+5	Loss	Sl.	.....	Neg.	Vert. C.	27.0	
J. G. K.	M.	W	32	+2	Gain	Sl.	.....	SR.	Diag. C.	20.5	
F. B.	F.	W	30	+5	Gain	Sl.	.....	SR.	Diag. C.	25.0	
M. Q.	F.	W	24	+6	Const.	Sl.	Hemoptysis	MR.	Diag. C.	22.0	
T. G.	M.	W	36	+6	Loss	Sl	Art. pneumothorax, hemoptysis, pneumonokoniosis	MR.	Diag. C.	24.0	
G. K.	M.	W	37	+4	Gain	Sl.	Hemoptysis	MR.	Diag. C.	24.5	Bone tuberculosis
H. P.	F.	W	19	+16	Gain	Sl.	.....	MR.	Diag. C.	26.0	
C. D.	M.	W	32	+5	Loss	Sl.	Hemoptysis, pneumonokoniosis	MR.	Diag. C.	26.5	
L. B.	F.	W	23	+2	Loss	Sl.	Hemoptysis	MR.	Diag. C.	28.0	
W. H.	M.	B	31	+8	Loss	Sl.	.....	MR.	Diag. C.	29.0	
R. R.	M.	W	41	+3	Gain	Norm.	.....	HR.	Diag. L.	11.0	
R. K.	M.	W	23	+2	Loss	Norm.	Hemoptysis, ischiorectal abs.	HR.	Diag. L.	12.0	
A. McE.	M.	W	50	+8	Gain	Sl.	.....	HR.	Diag. C.	21.0	
F. W.	M.	W	34	+5	Loss	Sl.	Hemoptysis	HR.	Diag. C.	21.0	
A. Y.	M.	W	14	+2	Const.	Sl.	Pleural effusion	HR.	Diag. C.	22.5	
F. C.	F.	W	29	+4	Gain	Sl.	Hemoptysis	HR.	Diag. C.	23.0	
A. M.	M.	W	42	+5	Const.	Sl.	Hemoptysis	HR.	Diag. C.	23.0	
B. DeP.	M.	W	46	+2	Loss	Sl.	Hemoptysis, pneumonokoniosis	HR.	Diag. C.	23.5	
R. N.	F.	W	50	+4	Loss	Sl.	.....	HR.	Diag. C.	24.0	
J. G.	M.	W	23	+5	Loss	Sl.	Hemoptysis, cold abscess	HR.	Diag. C.	25.0	
A. K.	M.	W	42	+2	Gain	Sl.	Syphilis	HR.	Diag. C.	25.0	
M. G.	F.	W	31	+7	Loss	Sl.	Hemoptysis, cervical adenitis	HR.	Diag. C.	26.0	
E. N.	F.	W	38	+4	Gain	Sl.	Hemoptysis	HR.	Diag. C.	27.0	
J. C.	M.	W	42	+7	Gain	Sl.	.....	HR.	Vert. C.	28.0	
F. S.	M.	W	32	+7	Gain	Sl.	Syphilis	HR.	Vert. C.	28.0	
A. S.	F.	W	41	+3	Loss	Sl.	.....	HR.	Vert. C.	35.0	

TABLE IX.—FAR-ADVANCED "C" CASES.

Name.	Sex.	Race.	Age.	Sputum.	Weight.	Temperature.	Complications.	Tuberculmet.	Sedimentation.		Remarks.
									Curve.	Amount, mm.	
L. DeJ.	M.	W	30	...	Loss	Sl.	Hemoptysis	Neg.	Diag. L.	16.5	
S. H.	M.	W	58	+5	Loss	Sl.	.....	Neg.	Vert. C.	28.5	
A. J.	F.	B	23	+8	Loss	Mod.	.....	Neg.	Vert. C.	33.0	
M. Y.	M.	W	37	+2	Loss	Sl.	Empyema	SR.	Diag. C.	27.5	
W. R.	M.	W	16	+6	Gain	Sl.	Empyema	SR.	Diag. C.	28.0	
M. B.	F.	W	15	...	Loss	Sl.	Hemoptysis	SR.	Vert. C.	29.5	
J. D.	M.	W	26	+7	Loss	Mod.	Empyema	MR.	Not done		Died.
J. W.	M.	W	45	+3	Gain	Sl.	.....	MR.	Diag. C.	29.0	Died.
S. J.	M.	B	28	+5	Loss	Mod.	Nephritis	HR	Not done		
M. K.	M.	W	38	+2	Gain	Sl.	Hemoptysis	HR	Not done		
J. G.	M.	W	26	+7	Loss	Sl.	Nephritis	HR.	Hor. L.	4.0	
R. McC.	M.	W	23	+4	Loss	Sl.	Hemoptysis; hereditary syphilis	HR.	Hor. L.	8.0	Neg. 18 months.
M. G.	M.	W	49	+6	Loss	Sl.	.....	HR.	Diag. C.	30.0	
E. O.	M.	W	22	+4	Gain	Sl.	Pleural effusion	HR.	Vert. C.	29.5	

both of these patients were doing very poorly clinically, a fact which seems to contradict the test findings. One of these cases was complicated by syphilis. Of the remainder, 1 gave a diagonal curve and the other a vertical curve sedimentation; both had started a clinical down-hill course but not to an overwhelming extent.

Summary. Review of the 147 cases here presented shows that in 136 instances the combinations of the sedimentation and serum test results give, when interpreted in the light of the previously constructed scheme of possibilities, pictures which closely approximate those determinable by the usual methods of diagnosis (symptomatology, physical signs, sputum examination, Roentgen ray and so forth). In 11 cases only are the test findings at variance with the clinical condition as indicated by such methods. On analysis of these 11 cases it is found that 3 negative Tubercumet reactions (2 with diagonal line and 1 with vertical curve sedimentations) occurred in patients with apparently definite active tuberculosis and in whom there was no evidence of a sharp decline in condition; of these, however, 1, a Philippino, has always had negative sputum and is a possible case of mycotic infection. Two moderate positive Tubercumet reactions, in conjunction with horizontal and diagonal line sedimentation curves, respectively, occurred in patients with definitely advancing tuberculosis. Four patients presenting heavy positive Tubercumet reactions with horizontal or diagonal line sedimentation curves were thought to be quite definitely in the period of declining resistance and advancing infection. However, 1 of these now has negative sputum and is showing no signs of pathologic activity in the lungs, while another was recently discharged as "quiescent." Two cases had heavy positive reactions with vertical curve sedimentations in spite of the fact that there was, especially in 1 case, considerable advance in the disease process.

It is worthy of note here that the 5 patients of this series who had a definite syphilitic infection (evidenced by positive serological findings), all had heavy positive Tubercumet reactions. Furthermore, 4 of these are included in the 11 cases, the interpretations of whose test results conflict with the clinical findings.

Conclusions. We do not believe that one is truly justified in drawing conclusions as to the worth of this method from this single series of observations. The several chances for error in the individual tests and in the interpretation of the combined results, the comparatively small number of cases worked upon to date and the lack of basic knowledge of sedimentation and serum reaction phenomena preclude positive assertions. However, the fact is encouraging, that in this single series there is a rather high degree of correlation between the clinical condition of the individual patients and the results of the tests as interpreted in the arbitrarily constructed scheme here presented. The basic principles of the

sedimentation and Tubercumet reactions, the relation of syphilis to the serum reaction, and so forth, present subjects for further investigation.

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THE ARTIFICIAL PRODUCTION OF PUNCTATE BASOPHILIA AND RETICULATION IN ERYTHROCYTES.

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From the time Ehrlich (1885) noted the three distinct basophilic conditions in erythrocytes, controversies have waged on their character and significance; but for many years the trend of opinion has been toward the view that punctate basophilia, diffuse polychromasia and reticulation are expressions of the same process.

Cesaris-Demel (1907) concluded that punctate basophilia and reticulation are identical, and Key (1921) agrees that the basophilic substance in the three conditions is the same. Brookfield (1928) believes that the stippled cells in lead poisoning are immature cells (reticulocytes and polychromasic cells) altered by the toxic action of lead. His results tend to confirm the work of Hawes (1909) and Key (1924) in which the close numerical relationship between stippled and polychromasic cells and reticulocytes was definitely established.

The nature of the staining substance is still undetermined, nor has any explanation been offered as to why the different appearances occur. Pappenheim (1907) and Biondi (1908) independently propounded the view that the stainable substance is a dye precipitate upon the surface of the lipoid membrane, but later, Pappenheim (1919) rather altered this idea, and suggested that the lipoid component of the spongioplasm was the reacting substance.

That the substance is not chromatinic is beyond doubt. The staining reaction with methylene blue-eosin preparations and with methyl-green pyronin, the occasional appearance of the condition in normally nucleated erythrocytes, and the fact that none of

the conditions is visible by dark-ground illumination or ultraviolet light are among the arguments against punctate basophilia, polychromasia and reticulation being nuclear in origin.

Gruner (1913) suggested that the reticular substance is not nuclear but plasmatic in character because in embryos and young animals its abundance is not associated with the appearances of changes in the nucleus. I have confirmed this observation in cases of Addison's anemia during normoblastic crises, in von Jaksch's anemia and in myeloid leukemia. In these diseases there does not appear to be any relationship between the younger normoblasts and the older normoblasts and the amount of reticular substance.

The present work is an attempt to elucidate these problems. The fact that hemoglobin gives a characteristic reaction with benzidin and hydrogen peroxid was utilized to the exclusion of all other stains. Blood films were made on 3 by 1 microscope slides and allowed to dry in the air before treatment. By altering the quantities of the reagents,* it is possible to disturb the apparent homogeneity of the erythrocyte. For the better appreciation of the early effects we will take the final results first. Fig. 1 is a photomicrograph of erythrocytes from which the hemoglobin has been more or less completely discharged. Benzidin in alcohol and hydrogen peroxid were used in such strengths that when flooded on to the film a greenish precipitate was immediately produced from the released hemoglobin and floated to the surface. The reaction was allowed to continue for twenty minutes. If the corpuscles in the figure be examined with a hand lens an irregular meshwork is seen and the spaces between the strands have the appearance of pores. The outline of the cells is irregular but the mean diameter is increased. The probable sequence of events is that the lipoid membrane has been oxidized and dissolved, and a slow fixation has brought into evidence a spongy stroma through the interstices of which the reagents have penetrated. Reaction between the benzidin and hydrogen peroxid and hemoglobin has taken place with solution and escape of the end product. Having seen the end result, all kinds of patterns, depending upon the varying degrees of penetration of the envelope and the amount of hemoglobin released, would appear possible. This is, in fact, true. Every type of punctate basophilia and reticulation may be duplicated.

Fig. 2 is an example of punctate basophilia of the fine type. If the cells are examined with a lens it will be apparent that the reaction has not progressed to the stage of Fig. 1. There are areas in which the granules are sharply defined but in others they are blurred in outline, suggesting that the hemoglobin has been reached but different stages of the reaction taken place.

* The reagents are benzidin 0.01 per cent in 80 per cent alcohol and hydrogen peroxid.

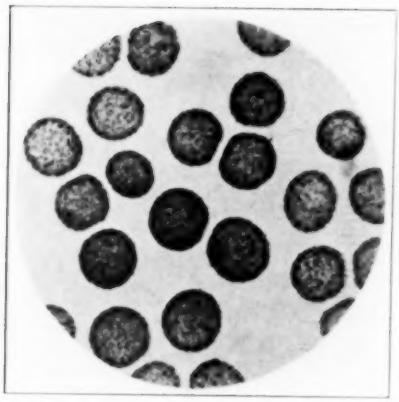

FIG. 1.—Erythrocytes showing spongioplasm after the lipoid membrane has been altered or dissolved. × 1000.

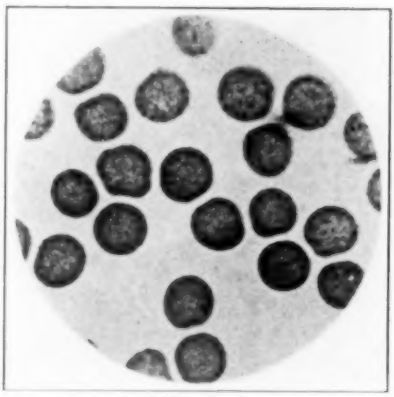

FIG. 2.—Erythrocytes showing finely granular punctate basophilia. × 1000.

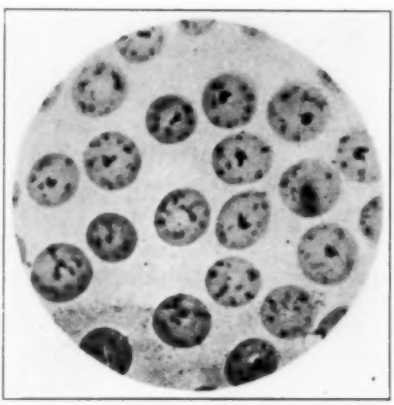

FIG. 3.—The clumped form of punctate basophilia showing granules of irregular shape. × 1000.

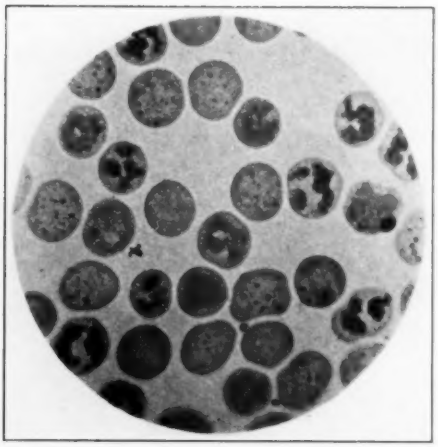

FIG. 4.—Punctate basophilis reticulation and diffuse polychromasia (x). × 1000.

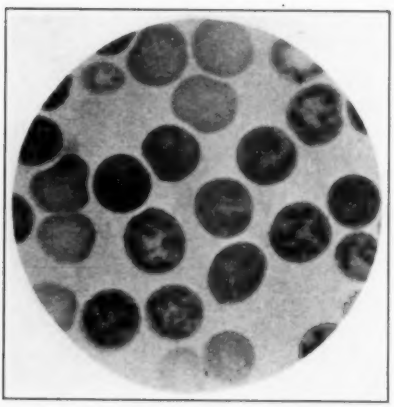

FIG. 5.—The bar form of reticulation. × 1000.

The granules may be fine, as in this figure, or coarse, as in some of the cells in Fig. 4, or they may be irregular in shape and aggregated into small clusters, as in Fig. 3.

At a further stage the hemoglobin has escaped through the pores and bridged over intervening strands of the stroma. Areas have coalesced in an irregular manner and the appearance of reticulation results, as shown in some of the cells in Fig. 4. Though the "granulofilamentous" picture characteristic of the vital staining methods is not reproduced here, it is obvious that no fundamental difference could be necessary for its production.

As may be imagined, it is difficult to get the granulofilamentous form of reticulation, but I have done so in an odd erythrocyte.

All the forms of reticulation described by Brookfield (1928) from the unfragmented reticulum to the bar form may be reproduced. Fig. 5 is an example of the bar form. The reticulocytes in Fig. 4 suggest that the next stage must be diffuse polychromasia. The cell marked *X* in Fig. 4 illustrates the condition up to a point, but there is a rim of unaffected material around the central stained area. This is probably due to the time given for the reaction being too short.

Summary.—This preliminary note is merely intended to place on record the fact that punctate basophilia, diffuse polychromasia and reticulation may be produced in any erythrocyte. The time is not opportune to enter into the discussion which these results open up, but two deductions may, I think, be made. The first, that with our previous knowledge of the staining reactions, the above results strengthen the belief that the stainable substance is not nuclear in character, but is probably a hemoglobin compound, and that the three basophilic conditions of the erythrocyte are qualitatively the same and vary only in degree or method of production.

The second deduction is that the conditions when obtained by the usual staining methods would point to increased permeability or a defect in the lipoid envelope of the erythrocyte. There may be, and probably is, a close relationship between punctate basophilia, diffuse polychromasia and reticulation and immaturity.

NOTE.—I must take this opportunity to express my thanks to my friend, C. F. Hill, for his invaluable assistance with the photomicrographs.

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POLIOMYELITIS.

Its Pre-paralytic Period with Results of Serum Therapy.* †

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This paper is the report of 126 cases of poliomyelitis seen in the pre-paralytic stage and treated by the intraspinal injection of human immune or convalescent serum and in few instances, by non-specific horse serum.

These cases occurred in the city of Syracuse or the surrounding territory during 1921 to 1926 inclusive, and were all seen by this observer in the capacity of private consultant or as consultant to the Syracuse Department of Health. This series is the largest number of such cases hitherto reported. It is felt that by it the value of intraspinal administration of serum to the early case is more definitely established, and, with our present knowledge of the disease is also demonstrated to be a proper therapeutic procedure. In the hands of this observer, such treatment in early cases of poliomyelitis has been apparently attended by most gratifying success and there is now no doubt in his mind as to its indication and value. Unfortunately, there are those who still think otherwise and controversy persists.

Surely the interpretation of results of any therapeutic procedure is often attended by difficulty. If such procedure were directed against a condition which, untreated, is characterized by 100 per cent mortality or 100 per cent development of uniform and characteristic sequelæ, then judgment would indeed be a simple matter. This, of course, is not true in poliomyelitis, as here the greatest variation exists in the severity of the case and in extent and distribution of the paralytic sequelæ, which range from the mildest type with only a simple muscle-group involvement to the fulminating tragic bulbar type, and to the more extensive paralyses of one or more extremities, 20 per cent of which end fatally. And then to make determination still more difficult, it may be that there are cases which do not develop paralysis at all and constitute the so-called abortive, evanescent, or nonparalytic type.

Generally speaking, and with the exception of the fulminating bulbar case, the pre-paralytic or febrile period is quite similar in all, and no one seeing a patient in this early stage can accurately prophesy the subsequent development. Consequently, it is here

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in this so-called abortive type that we find the great stumbling-block to satisfactory discussion and determination.

Nonparalytic Types. There are no accurate statistics available as the existence of such, but it is undoubtedly true that in the pandemic of 1916 such cases were seen with a roughly estimated incidence from 25 to 50 per cent. However, it is now felt that the percentage was then, and still is, greatly overestimated, and that its diagnosis was one most often made on only conjecture and hearsay. Abortive or nonparalytic cases, however, were definitely recognized in 1916 in Syracuse and vicinity, but only in small numbers and since then have been strikingly absent. In the writer's complete series of 340 cases since 1916, only 4 such have come to his attention, and, with inquiries among many physicians, it must be concluded that they are rare. Certainly, it cannot be that all the favorable cases of this treatment series were abortive cases and coincidentally treated and yet that is an argument that has to be met. This may be done quite conclusively by the fact that during the same five-year period 210 cases were also seen by this observer in the early hours of paralysis and in all of them the history of the same characteristic symptoms of the preparalytic period was obtained. Surely, were abortive or nonparalytic types numerically prevalent, their presence would have been quickly remarked, certainly in more than 4 instances.

Extent of Paralytic Involvement in Direct Ratio to Pre-paralytic Severity. This series may possibly represent some nonparalytic cases, but it is believed that most of the 126 were potentially true paralytic types and in most of, if not all, the 93 recoveries the therapy instituted prevented crippling sequelæ of variable degree, and some fatalities. Furthermore, it can be fairly said that many of this number represented the severer types of the disease, as the greater severity of their early symptomatology gave rise to the more immediate suspicion of the nature of the process and to the earlier diagnosis and treatment. Certainly, in the series of paralytic cases diagnosed only at the paralytic stage, it is quite evident that the extent of paralytic development was most often in direct ratio to the severity of the pre-paralytic symptoms.

Serum to the Paralyzed Case. Unfavorable opinion of serum therapy has been greatly engendered by the delayed and apparently unsuccessful administration in the presence of paralysis. It is then too late and, of course, unsuccessful. Certainly, paralysis once established cannot be greatly influenced by intraspinal serum and unless we have a case very early in this paralytic period, with continuing fever and persisting high cellular reaction in the spinal fluid, serum should not be given.

Early Access to Cases. In 1924, 133 cases with 12 deaths occurred in the city of Syracuse. Sixty-one were diagnosed in the pre-paralytic stage and given serum. Of these, 50 did not develop paralysis. This is pointed to with pride, but with the possible exception of 14

bulbar cases, all the others might have likewise been so diagnosed and treated. The early access to these cases was accomplished by newspaper publicity with the careful and conservative description to the public of the early symptoms, the advice to call the doctor immediately, and by the maintenance of consulting diagnosticians with available convalescent serum. It might be remarked that the death rate in this 1924 series was 9 per cent as compared with Syracuse figures of 28 per cent in 1916, 24 per cent in 1922, and 21 per cent in 1926. This, of course, is not alone conclusive argument for early serum treatment, but it must be given some consideration, as in no other series was there such a high percentage of early diagnoses.

Diagnosis. It is to be recalled that poliomyelitis is an acute infectious disease of the central nervous system and characterized by a very typical febrile period averaging three days in duration. This, in reality, is the active disease, although termed the pre-paralytic period. It ends quite abruptly with the appearance of paralysis of extremities or involvement of the motor cranial nerves and then, after a few hours (averaging twenty-four) for the complete institution of paralysis, the active disease is in reality over, and it becomes in comparison a passive problem in orthopedics.

The serum therapy of poliomyelitis necessitates its early diagnosis, that is, diagnosis in its pre-paralytic, febrile, or active period. This sometimes in sporadic cases may offer a perplexing problem to the attending physician, or even to the expert diagnostician. But rarely so. In former years diagnosis was made only on the appearance of paralysis, but with our present knowledge, there is certainly little excuse for missing cases, and in epidemic times it seems hardly justifiable that a pre-paralytic case should ever be mistaken.

It seems generally accepted that this disease is a systemic infection, but in the conception of this observer, it presents clearly a distinctive infection of the central nervous system with a pre-paralytic invasion of the meninges and a subsequent myelitis with its accompanying paralysis. It is indeed difficult for him to see it in the light of a systemic disease, as we ordinarily accept that classification.

Dromedary Type. However, as evidence of the possible systemic nature we should consider the dromedary type with an approximate incidence of 50 per cent. It is called dromedary because of the two humps or rises of temperature. Two to four days before the real beginning of the recognizable neurologic symptoms there may be a forty-eight-hour illness with fever, malaise, headache and vomiting. There is no rigidity of the neck, no tremor, and the general picture is that of an intestinal infection. The patient is usually in bed a day or two, then is apparently normal, until two to four days later, there is then developed the characteristic meningeal pre-paralytic picture. The initial "hump" of temperature may be interpreted as

evidence of preliminary intestinal infection with probable blood-stream invasion, a systemic disease. The subsequent, or second hump, representing its localization in the meninges and the initiation of the actual neurologic process. This type is also of especial interest in the consideration of the so-called abortive types. It is the author's opinion that there are many cases of this initial two-day illness which stop there and do not proceed to the further extension in the meninges. These then may constitute abortive cases, but they are never recognized as pre-paralytic poliomyelitis or so treated. The spinal fluid in three such cases has been examined by him and found entirely negative.

Symptoms and Signs. The pre-paralytic picture presents as a distinct clinical entity with symptoms definitely those of a mild meningitis; headache, tremor, and stiff neck constituting an outstanding triad.

Objective and subjective signs may be listed together as follows in order of importance:

1. *Fever.* Never high, with an average of 102° F.
2. *Headache.* Is severe; most frequently general, but may be nuchal and sometimes may be absent, but then replaced by severe back pain.
3. *Rigidity of the Neck.* Distinct resistance to anterior flexion. Rarely is there retraction and never lateral limitation.
4. *Tremor.* Fine trembling of lips and hands, especially on movement as when taking a glass of water. There may be also coarse twitching in sleep.
5. *Apathy.* The patients are mildy indifferent and drowsy—never comatose and are perfectly bright and alert when aroused, but then are sometimes irritable.
6. *Vomiting.* Once or twice on the first day, but rarely is it persistent or severe. It should be mentioned that vomiting is often severe as an initial symptom in the bulbar types.
7. *Retention of Urine.* When questioned, the mother often remarks a twelve- to twenty-hour period without urination; it never demands catheterization.
8. *Constipation.* It is almost uniformly present.
9. *Sweating.* This is usually seen as beading about the lips and neck, and is rarely profuse.

During this stage all movements of extremities are freely made and there is no great change in reflex or sensory status. It is to be forcefully emphasized that coma and convulsions, severe vomiting, diarrhea, chills and hyperpyrexia have never been observed by the author, and in his opinion, do not occur. In the bulbar type of case the pre-paralytic period is not so consistent and is much shorter in duration. In many such, there is difficulty in swallowing almost from the onset.

Spinal Fluid. With the exception of the bulbar and encephalitic types, this clinical picture is almost pathognomonic and is readily confirmed by lumbar puncture and here we find actual proof of the underlying meningeal pathology. This is in the pleocytosis of the fluid, the average count being 350 to the cubic millimeter. The pressure is slightly increased, and the fluid grossly shows varying degrees of turbidity. A 200 count seems, at first glance, as a clear fluid, but a distinct shimmer can be made out when carefully compared with the normal tube; with 350 cells there is a slight opalescence; with 500 a distinct opalescence, and at 1000 there is turbidity, indistinguishable from that of a suppurative meningitis. Microscopically, the type and proportion of cells varies; in severe cases in the first twenty-four hours the "polys" may predominate, but later the lymphocyte and an ependymal cell are the prevailing forms. Globulin or protein is, of course, consistently increased. The average fluid findings may be simulated in tuberculous, luetic and mumps meningitis, but such rarely give rise to confusion.

It is urged that fluid examination be made at the bedside. The number of cells can be immediately determined and the increase of globulin can be ascertained by the simple alcoholic precipitation test. Then, with such fluid confirmation, treatment can be instituted immediately. It is a great mistake to send the fluid to a nearby or distant laboratory and then await their report for a diagnosis of poliomyelitis, such delay may well be fatal.

Again, it is emphasized that poliomyelitis can be and should be diagnosed in this stage and before the ensuing paralysis makes it clear to all. With the development of paralysis, the fluid coincidentally shows the rapid disappearance of cells and in three or four days it is cell-free but with some persisting increase of protein. Hence, in older textbooks, the spinal fluids were reported as not remarkable, this, of course, being due to the fact that they were the fluids only from the paralyzed cases, with a then inactive pathology in the meninges.

Serum Treatment. Experimentally, the neutralizing or protecting power of human immune serum has been conclusively proved. In 1910, Levaditi and Landsteiner, Flexner and Lewis, and others demonstrated that 1 cc. of human or monkey convalescent serum rubbed up with 0.3 cc. of cord suspension, a fatal dose of virus, would neutralize that virus *in vitro*, in that this combined intradural implantation in monkeys was not followed by the otherwise usual development of the disease. Also, twenty-four hours after the intradural injection of a fatal dose of virus, 10 cc. of convalescent serum given intraspinally likewise protected the monkey from paralysis. Injections of serum given later than twenty-four hours were not so successful in aborting the process. These experimental results were at once utilized as a basis of serum therapy in man.

The method is as follows: Blood is collected with aseptic pre-

caution from individuals who have recovered from the disease preferably within a four-year period. However, donors, with their paralyses of twenty years' standing, were also used, and without any apparent difference in results. The serum is carefully separated and inactivated; to it may be added as a preservative 0.2 per cent tri-cresol. In Syracuse, this serum was obtained by advertising and paying for it. Two hundred and fifty cubic centimeters were taken from adult individuals, and from this 100 cc. of clear serum were usually obtainable.

Its administration in this series has been entirely intraspinally. It is given by gravity after the removal of a greater amount of fluid, but drainage is continued until definite nuchal pain is complained of. The amounts of serum given vary from 10 to 25 cc., according to the size and age of individual. It is now believed that one mistake of the earlier cases was too small dosage; 10 cc. in an infant is not too large, and 25 cc. should be given to the vigorous adult.

The opportunity is taken here to emphasize the fact that serum treatment necessitates lumbar puncture, and, although in the hands of the experienced, a simple procedure, it can become a very disturbing and distressing one in the hands of others. The man who, with grim determination, proceeds to make a colander of the back of a struggling and suffering child may well produce much more harm than his serum can do good. The importance of proper position of the patient, the preliminary use of novocain and a small 19- to 20-gauge lumbar puncture needle, sharp and free from rust, needs hardly to be mentioned. A child or adult should rarely be hurt with lumbar puncture. Anesthetics are seldom necessary and are advised against, as it is believed that anesthesia renders the nerve cells less resistant to invasion of the virus.

Reactions. Mild reactions may follow the administration of human convalescent serum. This is in the nature of increased elevation of temperature four to eight hours after, and the accentuation of headache, back pains and restlessness. Such reactions are never dangerous and no untoward effect has ever been noted by this observer, however, it is strongly urged that the pain and restlessness be controlled by opiates—*the child must be kept quiet!* Also, the importance of proper nursing and careful observation cannot be overemphasized. Temperature should be taken every two hours. From the twelfth to twentieth hours after serum, observations should be made every hour.

Second Serum Administration. The decision for repeat of serum is often a delicate one and much depends upon the accuracy of observation. In this series, where possible, serum was repeated when temperature observations at the eighteenth to twentieth hour showed fever of 101° F. or more. The spinal fluid is usually cloudy from the first serum and is no true index of activity. However, some observers advise the serum administration only as the cell counts are 200 or over. The determination by temperature is considered the

safest determination. This decision should mainly rest with the consultant, who should again see the patient at this period. There is rarely the opportunity of a third dose as the patient is either paralyzed or recovered after a second. Again, the attending physician must watch his case. The time element is short, the potentialities are grave and his responsibility is great. Temporization, with "waiting till tomorrow" is often disastrous.

Results. In 1916, during the hectic days of that epidemic, 36 early cases were treated with intraspinal serum by this observer; 19 cases cleared without paralysis. Cases were then poorly checked and often only seen once. Sometimes, due to the lack of immediately available human convalescent serum, normal human, pneumococcic, and normal horse serum were given, and given mainly on an empirical basis, but surprisingly, often with equally favorably results. These nonspecific results and the then reported high incidence of the abortive case made analysis difficult and the author, with other field workers, was somewhat guarded in his opinion feeling that such recoveries might be coincidental, but since that time and mainly by the experience here presented, he is now convinced as to the value of serum treatment and earnestly advises it as the proper procedure in the early period of this disease.

The table of 126 cases is here presented for appraisal. They are grouped by year, 1921 to 1926 inclusive, and for each year the cases are tabulated in order of the duration hour arranged with the clinical findings, fluid findings, serum administered and results.

It is to be noted that there are comparatively few paralyses in those cases seen in the first twenty-four hours from onset. Of these 126 cases, there were 8 deaths, as follows:

Reports of Fatal Cases. Case 6.—Jack F., aged four and a half years, received 8 cc. of human immune serum at twenty hours. A second dose was urged at forty-four hours, but permission was refused. On the third day, in the presence of beginning paralysis, serum was then repeated at the request of the parents and attending physician. This was done under an anesthetic, also at their request. The child died the following day with paralysis of all extremities, a cervical respiratory death.

Case 7.—Ellwyn C., aged seventeen years, seen at twenty-six hours, received 15 cc. human immune serum; fourteen hours later beginning paralysis of uppers appeared and no additional serum was given. Paralysis gradually extended to all extremities with cervical respiratory death on the fifth day. This was a frank disappointment. It is of interest to note that this patient was a muscular truck driver and determinedly kept driving through a cold, rainy day during the first twelve hours of illness.

Case 64.—Andrew D., aged sixteen years, was seen at thirty hours with a second dose given at fifty-four hours. The interesting finding here was an absence of the usual reaction to the first serum as shown by the low cells in the second puncture. This boy was, likewise, a great disappointment, as two doses of serum were given in satisfactory amounts, at proper intervals and without apparent benefit.

POLIOMYELITIS — PREPARALYTIC STAGE.

(Results of Intraspinal Serum Therapy.)

1921

15 Cases reported in Syracuse—2 deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Duration.	Temp.	Pulse.	Headache.	Neck.	Tremor.	Apathy.	Spinal fluid. Cells.	Polys.	Lympho.	Protein.	Serum.	Results.
1	Oct. 12	Stephen M.	Syracuse	Luke	15	5 hrs.	103	—	++++	++++	++++	++++	350	57%	38%	++++	12 cc. Pn.	No paralysis.
2	Sept. 28	Donald G.	Syracuse	Lawless	5	26 hrs.	104—	120	++	++++	++	++++	210	—	90%	+++	6 cc. Pn.	No paralysis.

1922

46 Cases in Syracuse—11 Deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Duration.	Temp.	Pulse.	Headache.	Neck.	Tremor.	Apathy.	Spinal fluid. Cells.	Polys.	Lympho.	Protein.	Serum.	Results.
3	Sept. 21	James W.	Syracuse	Mesick	4	14 hrs.	102 5	—	+?	++++	++++	++++	20	Lymphocytosis		++++	15 cc. H.I.	No paralysis.
4	Sept. 2	Laura R.	Fabius	Gossner	15	15 hrs.	101	100	++	++	O	+	50	Lymphocytosis		++++	15 cc. H.I.	No paralysis.
5	Sept. 12	Henry M.	Liverpool	Platner	4	20 hrs.	103 6	152	++++	++++	++++	++++	320	—	—	++++	15 cc. Pn.	No paralysis.
6	Oct. 11	*Jack F.*§	*Syracuse*	*Wynkoop*	4½	20 hrs.	102 6	136	++++	++++	++++	++++	500	—	95%	++++	8 cc. H.I.	*Extensive paralysis.*§
						68 hrs.	102	Beginning paralysis of all extremities					200	—	—	++++	8 cc. H.I.	*Exodus at 90 hours.*
7	Oct. 19	*Ellwyn C.*§	*Syracuse*	*Harter*	17	26 hrs.	102	100	++++	++++	++	++	360	—	—	++++	15 cc. H.I.	*Extensive paralysis.*§
						40 hrs.	Beginning paralysis —left shoulder —no additional serum given										*Exodus in 5 days.*
8	Sept. 11	Dorothy K.	Syracuse	Bamford	6	34 hrs.	102	—	++++	++++	++++	++++	220	—	—	++++	10 cc. H.I.	No paralysis.
9	Oct. 9*	James W.	Apulia	Padgett	13	34 hrs.	101	136	++++	++	+	+++	160	—	—	++++	10 cc. H.I.	Weakness right quadriceps.*
10	Aug. 29*	Robert G.	Eastwood	Seagfrid	6	36 hrs.	103	—	++++	++++	++++	++++	250	—	—	++++	15 cc. Pn.	Paralysis right shoulder.*
11	Sept. 8	Josephine H.	Syracuse	Mitchell	2	36 hrs.	101	—	?	++++	+	+++	160	—	—	++++	15 cc. H.I.	No paralysis.
12	May 21	Dwight C.‡	Syracuse	Sharkey	7	36 hrs.	102 4	140	++++	++++	++++	++++	140	—	—	++++	10 cc. Pn.	Paralysis both
						56 hrs.	101 4	112	+	++++	+	++++	Cloudy	90%			12 cc. H.I.	arms, one lower.‡
13	Oct. 14	Hazel D.	Fabius	Gossner	10	40 hrs.	101 3	104	++++	++++	++++	++++	250	—	—	++++	16 cc. H.I.	No paralysis.
14	Sept. 13	James H.	Fabius	Gossner	12	40 hrs.	103	130	++++	++++	++++	++	160	—	—	+++	15 cc. H.I.	No paralysis.
						67 hrs.	101 8	—	O	++++	+	++++	Cloudy	Fluid— Low pressure			5 cc. Pn.	
15	Oct. 17	Leslie C.	Apulia	Padgett	16	48 hrs.	101	194	++++	++++	++++	+	90	—	—	++++	12 cc. H.I.	No paralysis.

1923

8 Cases in Syracuse—1 death.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Duration.	Temp.	Pulse.	Headache.	Neck.	Tremor.	Apathy.	Spinal fluid. Cells.	Polys.	Lympho.	Protein.	Serum.	Results.
16	Aug. 8	Charles B.	Syracuse	Wood	5	20 hrs.	102 1	138	+++	++++	++++	++	760	94%	6%	++++	10 cc. Pn.	No paralysis.
17	Sept. 9	John G.	Liverpool	Platner	6	32 hrs.	102	—	++	++++	++++	++	160	—	—	++	10 cc. Pn.	No paralysis.

*—Muscular weakness—clearing in six months—13 cases.
†—Paralysis of moderate degree—residual in one extremity—9 cases.
‡—Severe paralysis with permanent involvement of more than one extremity—4 cases.
§—Deaths in italics—8 cases.

Pn.—Pneumococcic serum
H. I.—Human immune

93 cases cleared without paralysis.
46 cases seen within the first twenty-four hours.

POLIOMYELITIS—PREPARALYTIC STAGE.—(*Continued.*)

1924

133 Cases in Syracuse—12 Deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Duration.	Temp.	Pulse.	Headache.	Neck.	Tremor.	Apathy.	Spinal Fluid. Cells.	Polys.	Lympho.	Protein.	Serum.	Results.
18	June 29	Donald A.	Syracuse	Palmer	9	5 hrs.	102	130	++++	++++	++++	+	620	60%	40%	++++	10 cc. Pn.	No paralysis.
						25 hrs.	101	120	++++	++++	+	++++	Cloudy	100%		—	10 cc. Pn.	(Serum react. ++).
19	Aug. 20	Eugene H.	Manlius	Curtiss	11	6 hrs.	102.2	—	++++	++++	++	++	240	—	90%	++++	10 cc. Pn.	No paralysis.
20	July 23	Dorothy W.*	Syracuse	Ransom	6	6 hrs.	102	140	+	++++	++++	++	350	—	—	++++	10 cc. Pn.	Sl. weakness right quadriceps.*
21	Aug. 5	Chas. W.	Syracuse	Coomes	9	8 hrs.	102.2	136	++++	++++	++++	+	300	90%	10%	++++	10 cc. H.I.	No paralysis.
						32 hrs.	101	130	++	++++	+	++++	Bloody			—	10 cc. Pn.	(Serum react. ++).
22	Sept. 17	Paul M.	Syracuse	Cave	5	10 hrs.	100.8	134	++++	++	O	+	60	Lymphocytosis		.+++	10 cc. H.I.	No paralysis.
23	Aug. 6	Raymond S.	Syracuse	Ayling	4	10 hrs.	102	140	++	++++	O	+++	65	—	—	++++	10 cc. H.I.	No paralysis.
24	Aug. 24	Robt. F.	Syracuse	Babcock	2	12 hrs.	101	120	?	++++	+++	++++	280	15%	25%	++++	10 cc. H.I.	No paralysis.
25	Aug. 11	Basil R.‡	Syracuse	Cave	10	12 hrs.	101.4	120	++++	++++	+	+++	600	20%	80%	+++	10 cc. Pn.	Extensive descending paralysis.‡
						32 hrs.	Temp. reported as normal and boy much improved—at 70 hrs. temp. 103												Survival.
26	Aug. 21	Mary E.	E. Syracuse	Marsh	7	12 hrs.	101	144	++	++++	+	+	220	—	—	++++	12 cc. H.I.	No paralysis.
27	Aug. 26	Elizabeth W.	Syracuse	Lawless	16	12 hrs.	100.4	102	++++	++	O	O	190		+90%	++	15 cc. H.I.	No paralysis.
28	Aug. 30	Carl G.	E. Syracuse	Synder	4	15 hrs.	100.2	—	++	++++	+++	++++	360	—	—	++++	6 cc. Pn.	No paralysis.
29	July 19	William S.	Syracuse	Blodgett	5	15 hrs.	102	124	++++	++	O	++++	90?	Bloody	—	++++	8 cc. H.I.	No paralysis.
30	Aug. 5	Irma C.	Syracuse	Brougham	13	16 hrs.	102	130	+++	+++	++	++++	320	20%	80%	++++	10 cc. H.I.	No paralysis.
31	Aug. 4	Wm. L.	Eastwood	Marsh	7	16 hrs.	102	128	++++	++++	++++	O	280	15%	85%	++++	10 cc. H.I.	No paralysis.
						36 hrs.	101	100	+	++++	+	++	1380	90%	—	++++	8 cc. Pn.	(Serum react. +).
32	Aug. 16	Rose McD.	Syracuse	Larned	4	18 hrs.	102	120	+++	++++	+++	++++	200	—	—	++++	8 cc. Pn.	No paralysis.
						38 hrs.	101.2	100	+	++++	O	++++	Turbid	95%	—	++++	6 cc. Pn.	
33	Aug. 25	James H.	Syracuse	Wood	6	18 hrs.	101.4	130	++++	++++	+	++++	120	—	90%	++++	12 cc. H.I.	No paralysis.
34	July 26	Bernard G.	E. Syracuse	Seagfrid	8	20 hrs.	102	112	+++	++++	++++	+	80	—	90%	++++	10 cc. H.I.	No paralysis.
35	July 30	Carl G.	E. Syracuse	Seagfrid	13	20 hrs.	99.6	110	++	++++	+	+	100	—	90%	++++	10 cc. H.I.	No paralysis.
36	Aug. 20	Marvin H.*	Jordan	Dye	13	20 hrs.	101	130	++++	++++	+++	++++	460	80%	20%	++++	12 cc. H.I.	Weakness back and lowers.*
37	July 11	John M.	Syracuse	Lynch	6	20 hrs.	101.6	154	+	++++	O	++	90	—	—	++++	10 cc. Pn.	No paralysis.
						44 hrs.	100.4	—	++	++++	++	++++	260	—	—	++++	10 cc. H.I.	
38	Aug. 12	Theodore S.	E. Syracuse	Snyder	23	21 hrs.	101.4	104	++++	++++	++++	++++	40	20%	80%	?	—	No paralysis.
						27 hrs.	102.0	120	++++	++++	++	++++	180	—	—	++++	15 cc. H.I.	
39	Aug. 16	John A.	Eastwood	Luby	3	20 hrs.	101	160	++++	++++	+++	++++	140	—	90%	++++	8 cc. Pn.	No paralysis.
40	Aug. 19	Howard B.	Syracuse	Foreman	24	20 hrs.	101.8	130	++++	++++	+++	++	210	—	—	++++	15 cc. Pn.	No paralysis.
41	Aug. 30	Peggy C.	Syracuse	Lawless	11	20 hrs.	101.2	130	+++	+++	O-?	+	280	—	—	++++	15 cc. H.I.	No paralysis.
42	July 21	Donald D.	Syracuse	Berman	7	20 hrs.	103	132	++	++++	++	++++	210	—	—	++++	10 cc. H.I.	No paralysis.
43	July 25	Dorothy G.*	E. Syracuse	Snyder	6	20 hrs.	102.2	130	++	++++	++++	++++	200	10%	90%	++++	10 cc. Pn.	Slight quadriceps
						44 hrs.	103.0	120	+++	++++	+	++	Turbid			++++	10 cc. Pn.	weakness.*
44	July 31	Hubert H.	E. Syracuse	Richardson	6	20 hrs.	103	104	++++	++++	++++	++++	410	—	—	++++	12 cc. H.I.	No paralysis.
45	Aug. 17	Ralph W.	New Haven	Goewey	6	20 hrs.	103		+++	++++	++++	++++	280	—	—	++++	10 cc. Pn.	No paralysis.
						48 hrs.	102		++++	++++	++++	+	800	50%	50%	++++	15 cc. Pn.	
46	July 30	Rosetta G.	Pleasant Beach	Mahar	9	24 hrs.	102	130	++++	++++	++++	++++	250	—	—	++++	15 cc. H.I.	No paralysis.
						42 hrs.	100.2	—	—	++++	—	++++	Turbid	—	—	—	15 cc. H.I.	
47	Aug. 21	Disque D.	Cazenovia	Joy	3	24 hrs.	101	140	++++	++++	O	+++	240	—	—	++++	10 cc. H.I.	No paralysis.

47	Aug.	21	Disque D.	Cazenovia	Joy	3	24 hrs.	101	140	++++	++++	O	+++	240	–	–	++++	10 cc. H.I.	No paralysis.	
48	July	9	Ralph H.†	Syracuse	Larned	5	24 hrs.	101.4	140	++++	++++	++++	++++	360	75%	75%	++++	10 cc. Pn.	Paralysis of left shoulder.†	
							48 hrs.	103	148	++++	++++	++++	++++	Turbid	–	–	–	10 cc. Pn.		
49	Aug.	9	Dora B.	Fayetteville	Bryant	14	24 hrs.	99.4	104	++++	++++	+	O	90	–	90%	++++	6 cc. H.I.	No paralysis.	
50	Sept.	23	Ed. W.	Syracuse	Mahoney	14	20 hrs.	101	130	++++	+++	++++	+++	420	30%	70%	++++	20 cc. H.I.	No paralysis.	
							40 hrs.	101	102	+	++++	++++	+	Turbid	90%	–	–	20 cc. H.I.		
51	Aug.	14	Henry J.	Syracuse	Frye	9	24 hrs.	101.4	104	++++	++++	O	++++	160	–	–	++++	6 cc. Pn.	No paralysis.	
52	July	21	Thos. S.	Syracuse	Mesick	3	24 hrs.	100.4	140	?	++++	++	++++	110	–	–	++++	10 cc. H.I.	No paralysis.	
							36 hrs.	101.2	144	?	++++	O	++++	Cloudy	–			10 cc. H.I.		
53	Sept.	3	Ernest J.	Fabius	Gossner	13	24 hrs.	102	–	++++	++++	+++	++	800	50%	50%	++++	15 cc. H.I.	No paralysis.	
54	July	22	Geo. C.	Syracuse	Mahar	5	26 hrs.	102.4	130	+++	++++	+++	++	480	–	–	++++	7 cc. Pn.	No paralysis.	
							48 hrs.	101	140	+	++++	++++	O	Cloudy	–	–	–	10 cc. H.I.		
55	Oct.	20	Isabel W.*	Canastota	Warner	6	26 hrs.	101.4	130	++	+++	++++	+++	150	–	–	++++	10 cc. H.I.	Weakness **right** shoulder.*	
56	Aug.	25	Clarence N.	Syracuse	Wood	6	26 hrs.	102	130	+++	++++	+++	+	220	–	–	++++	10 cc. H.I.	No paralysis.	
57	June	8	Joseph G.	Syracuse	C. Smith	8	26 hrs.	103	132	++++	++++	O	++++	360	25%	75%	++++	10 cc. Pn.	No paralysis.	
							48 hrs.	102	120	++	++++	+++	+	Turbid	100%	–	++++	10 cc. Pn.		
58	Aug.	22	Evelyn I.*	Memphis	Dye	9	26 hrs.	102	–	++++	++++	O	+	280	20%	80%	++++	10 cc. H.I.	Weakness both quadriceps.*	
59	Oct.	20	Jane K.	Syracuse	Heath	6	28 hrs.	102	130	+++	++++	O	O	180	–	–	++++	15 cc.	No paralysis.	
60	Aug.	19	Clement Z.	La Fayette	Williams	14	28 hrs.	101.5	–	+++	++++	+++	+++	680	–	90%	++++	20 cc. H.I.	No paralysis.	
61	Aug.	26	Leo G.†	New Haven	Goewey	32	28 hrs.	102.3	110	++++	++++	++++	O	160	–	–	++++	15 cc. H.I.	Paralysis **right** shoulder.†	
62	Aug.	2	Edith McC.	Syracuse	Magee	6	28 hrs.	102	150	+++	O	+	+	360	–	–	++++	6 cc. H.I.	No paralysis.	
63	Sept.	6	James Van D.	Jordan	Dye	19	28 hrs.	99.8	120	++	++++	+	++	160	–	–	++++	15 cc. H.I.	No paralysis.	
64	July	22	Edwin W.	Syracuse	Ransom	3	28 hrs.	101	120	+++	++	+	O	140	–	–	++++	5 cc. H.I.	No paralysis.	
65	July	31	Chas. F. S.	Syracuse	Ayer	4½	30 hrs.	102.4	148	++	++++	++++	++++	160	40%	60%	++++	8 cc. Pn.	No paralysis.	
66	Sept.	26	Jennie A.*	Canastota	Warner	24	30 hrs.	100.2	130	+++	++++	+++	O	800	–	–	++++	15 cc. H.I.	Paralysis **right** quadriceps.*	
67	Aug.	1	*Andrew J.§*	*Syracuse*	*Larned*	16	30 hrs.	102	100	++++	++++	++++	O	620	–	90%	++++	15 cc. H.I.	*Extensive paralysis 60 hrs.§*	
							54 hrs.	101	112	+	++++	O	++	260	–	95%	++++	20 cc. H.I.	*Death 90 hours.*	
68	Aug.	13	Francis McK.	Syracuse	Donegan	5	30 hrs.	201	140	++++	++++	++++	++++	320	–	–	++++	10 cc. H.I.	No paralysis.	
69	July	29	Wm. H.	Syracuse	Mahoney	3	30 hrs.	101	140	++++	++++	++	++++	220	–	–	++++	8 cc. H.I.	No paralysis.	
70	Oct.	2	Esther H.	Cazenovia	Joy	18	32 hrs.	100.3	100	+++	++++	++++	O	320	–	–	++++	15 cc. H.I.	No paralysis.	
71	Aug.	22	David Van K.	Syracuse	Potter	6	32 hrs.	101.4	130	++++	++++	++++	+	160	–	90%	++++	12 cc. Pn.	No paralysis.	
72	Aug.	25	Arch. McD.	Syracuse	Shepard	17	36 hrs.	102	130	++	++	++	++	70	–	–	++++	10 cc. H.I.	No paralysis.	
73	Aug.	10	Melva W.	New Haven	Goewey	6	36 hrs.	102	112	++	++++	++++	++++	320	35%	65%	++++	10 cc. H.I.	No paralysis.	
74	Oct.	20	LaRue W.	Auburn	Sincerbeaux	5	36 hrs.	102	130	++++	+++	++++	+++	700	25%	75%	++++	10 cc. H.I.	No paralysis.	
							50 hrs.	101.4	124	+	++++	+	+	Turbid	95%	–	++++	10 cc. H.I.		
75	Aug.	19	Jack G.	Brewerton	Strong	12	36 hrs.	102	140	++++	++++	+	++++	290	–	–	++++	12 cc. H.I.	No paralysis.	
76	Aug.	9	Roberta Y.	Syracuse	Ehegartner	9	46 hrs.	101.2	118	+++	?	++++	+++	160	–	90%	+++	10 cc. H.I.	No paralysis.	
77	Aug.	11	Frank S.	Syracuse	Chiarulli	1½	48 hrs.	99	120	?	+	+++	++++	75	–	90%	++	6 cc. H.I.	No paralysis.	
78	Oct.	8	Willis A. B.	Syracuse	Du Bois	13	48 hrs.	100.4	112	+++	++++	O	O	150	–	90%	++	15 cc. H.I.	No paralysis.	
79	Sept.	30	Wm. C.	Auburn	O'Neil	25	48 hrs.	100.2	148	+	++++	+++	O	420	25%	75%	++++	20 cc. H.I.	No paralysis.	
							68 hrs.	101	130	++++	+++++	++++	O	Cloudy	95%	–	–	15 cc. H.I.		
80	Oct.	17	Norman R.	Syracuse	Buechler	8	48 hrs.	100.4	130	O	++	O	O	180	90%	10%	++++	15 cc. H.I.	No paralysis.	
81	Sept.	17	Ruth S.†	Fulton	Simpson	15	48 hrs.	100.4	132	+++	+++	O	O	160	–	90%	++++	15 cc. H.I.	Paralysis left upper.†	
82	Aug.	18	Dora I.	Memphis	Dye	5	48 hrs.	103	136	++++	+++	++	+	110	–	90%	++++	15 cc. H.I.	No paralysis.	
83	July	26	Oran B.	Syracuse	Herbert	1 2 mo.	48 hrs.	102	–	?	++++	+++	+++	180	–	–	++++	6 cc. H.I.	No paralysis.	
84	Aug.	24	D. D.	Clay	Winne	13	48 hrs.	101.4	130	+++	++++	+++	++++	160	–	90%	++++	10 cc. Pn.	No paralysis.	
85	Aug.	11	Betty J. H.	Syracuse	Street	5½	48 hrs.	101.3	–	+++	+	O	+	420	–	90%	++++	10 cc. H.I.	No paralysis.	
86	Sept.	3	Francis G.	Syracuse	Swift	21	50 hrs.	103	–	++++	++++	++++	++	620	–	–	++++	15 cc. H.I.	No paralysis.	
							70 hrs.	102	–	+	++++	++	O	200	–	–	–	20 cc. H.I.		
87	Oct.	14	Ida Marie D.†	New Haven	Philo	10	52 hrs.	100.1	120	+++	++++	O	++	180	–	95%	++++	15 cc. H.I.	Paralysis, one lower.†	
88	July	18	Robt. H.	Syracuse	Blodgett	7	54 hrs.	102	150	+++	++++	+++	++++	220	–	–	++++	10 cc. Pn.	No paralysis.	
							72 hrs.	102	136	O	++++	++++	++++	Turbid	90%		–	12 cc. H.I.		
89	Oct.	9	Nita P.‡	Brewerton	Strong	17	50 hrs.	101.4	120	++++	++++	+++	O	640	15%	85%	+	20 cc. H.I.	Paralysis **right shoulder**, right lower.‡	

POLIOMYELITIS—PREPARALYTIC STAGE.—(*Continued.*)

1925.
4 Cases in Syracuse—2 Deaths.

No.	Date.	Name.	Address.	Physician.	Age yrs.	Duration.	Temp.	Pulse.	Headache.	Neck.	Tremor.	Apathy.	Spinal Fluid. Cells.	Polys.	Lympho.	Protein.	Serum.	Results.
90	July 30	Wm. F.*	Syracuse	Newell	9	34 hrs.	101.2	124	+++	+++++	+	+++++	140	10%	90%	++++	10 cc. Pn.	Weakness rt. shoulder and back.*
91	Aug. 18	Austin C.*	Weedsport	St. John	12	36 hrs.	102.6	132	++++	+++++	++++	+++++	820	60%	40%	++++	12 cc. Pn.	Paralysis of left serratus.*
						55 hrs.	102	130	++++	++++	+	+	Turbid	100%	0%	—	15 cc. H.I.	
92	Sept. 21	Esther P.	Syracuse	Sorgues	4	36 hrs.	104	140	++++	+++++	++++	++++	800	35%	65%	++++	6 cc. A.M.	No paralysis.
						50 hrs.	102.8	140	++	++++	+	—	600	90%	10%	++++	6 cc. H.I.	
93	Dec. 19	Lois E.†	Cortland	Barker	3	36 hrs.	101.2	120	++	++++	O	++	210	—	—	++++	12 cc. H.I.	Paralysis right shoulder.†
94	Oct. 18	Betty Jane C.	Cuyler	Padgett	3	38 hrs.	102	150	O	++++	++++	++++	120	20%	80%	++++	8 cc. Pn.	No paralysis.
95	Sept. 16	*Grand MacD* §	*Syracuse*	*Burdick*	18	60 hrs.	102		++++	++++	++++	++++	820	74%	26%	++++	20 cc. Pn.	*Extensive paralysis, death at 8¼ hours.*§
						65 hrs.	Paralysis of right shoulder—rapid descending extension										

1926.
60 Cases in Syracuse—13 Deaths.

96	Aug. 18	Susanne L.	Syracuse	Smith	7	10 hrs.	100.8	104	+	+++++	++++	+	240	20%	80%	++++	12 cc. H.I.	No paralysis.
97	Aug. 23	Eloise C.	Syracuse	Evans	7	10 hrs.	103	156	++++	+++++	++++	++	740	50%	50%	++++	12 cc. H.I	No paralysis.
						32 hrs.	101.2	100	+	+++++	+	O	825	90%	10%	++++	10 cc. H.I.	
98	June 30	Cliff B.	Tully	Padgett	15	12 hrs.	103.2	108	+++	+++++	+++++		220	90%	10%	+	15 cc. Pn.	No paralysis.
						34 hrs.	104	108	O	+++++	O	++	430	—	—	+	15 cc. Pn.	
99	Sept. 15	Jane V.	E. Syracuse	Marsh	8	14 hrs.	101	136	+	+++++	+	++	120	—	—	++	10 cc. H.I.	No paralysis.
100	Sept. 10	Herbert H.	Warners	Coe	11	18 hrs.	102	126	+++	+++++	+++	+++	560	70%	30%	++++	13 cc. H.I.	No paralysis.
						46 hrs.	100.8	122	++++	+++++	+	++	Cloudy	90%	—	—	12 cc. H.I	
101	Sept. 6	Lucille H.*	Syracuse	Mahoney	12	20 hrs.	102	134	+++++	+++++	+++++	+++++	400	—	—	++++	13 cc. H.I.	Slight weakness in left shoulder.*
						42 hrs.	101	—	O	+++++	O	+	Cloudy	—	—	—	12 cc. H.I.	
102	Aug. 11	Helen O'H.	Syracuse	Lawless	12	20 hrs.	99.6	100	+	+++++	+	O	260	5%	95%	++++	15 cc. H.I.	No paralysis.
103	Aug. 11	Roy W.	Fabius	Gosner	8	22 hrs.	100.6	114	++++	+++++	++	+++++	120	70%	30%	++	12 cc. H.I.	No paralysis.
104	Aug. 4	Robert P.	Liverpool	Platner	9	20 hrs.	101.4	130	++++	+++++	+++++	+++++	820	90%	10%	++++	15 cc. H.I.	No paralysis.
						39 hrs.	102.4	122	+	+++++	++++	O	Cloudy	—	—		10 cc. H.I.	

105	July 23	James S.	Syracuse	Larned	7	24 hrs.	102	144	++	++++	+++	++	310	20%	80%	+++	15 cc. H.I.	No paralysis.
						44 hrs.	101.3	124	++	++++	+		4800	85%	15%	++++	75 cc. H.I.	
106	Sept. 8	Alice C.	Syracuse	Johnson	10	24 hrs.	101	96	++++	+	++	+++	330	—	—	++++	15 cc. H.I.	No paralysis.
107	Aug. 13	*Alfred M.*§	*Liverpool*	*Hagen*	7	24 hrs.	101	140	++++	++++	++++	++++	280	10%	90%	+++	10 cc. H.I.	*Respiratory death.*§
						48 hrs.	Reported much improved — Temperature normal — serum not repeated											
						72 hrs.	103	150	—paralysis of uppers, and respiratory				—death at 80 hrs.					
108	Aug. 7	Haumann F.	Syracuse	Heath	13	26 hrs.	99.8	76	+++	+++	+++	++++	260	10%	90%	+++	8 cc. Pn.	No paralysis.
109	Aug. 27	James B.	Syracuse	Newell	4	26 hrs.	102	156	+++	++++	++++	++++	110	85%	15%	++	12 cc. H.I.	No paralysis.
						42 hrs.	100.8	110	O	++++	+++		Cloudy fluid				12 cc. H.I.	
110	Oct. 9	*Alice S.*§	*Cortland*	*Brayman*	3	27 hrs.	101.1	148	++++	++++	++++	++	360	—	—	+	13 cc. H.I.	*Died; respiratory paralysis at 80 hours.*§
						51 hrs.	Reported as improved — normal temperature. No additional serum											
111	July 24	Ruth C.	Jordan	Dye	8	30 hrs.	100.4	140	+++	+	++	O	60	90%	10%	++	7 cc. H.I.	No paralysis.
112	Sept. 13	Alacia G.†	Marcellus	Parsons	18	30 hrs.	102.2	150	++	+++	++++	O	320	50%	50%	++++	15 cc. H.I.	Paralysis left shoulder.†
						51 hrs.	100.8	130	+++	++++	++	O	Turbid	90%	—		15 cc. H.I.	
113	Oct. 15	John P.	Homer	Forchee	4	32 hrs.	101.6	160	?	++	++	O	250	10%	90%	+	15 cc. H.I.	No paralysis.
						54 hrs.	101.6	110	O	++++	++	+++	Cloudy	90%	10%	+	10 cc. H.I.	
114	Aug. 12	Albert S.	Syracuse	Larned	17	36 hrs.	101	90	+++	++++	++++	++++	750	90%	10%	++++	20 cc. H.I.	No paralysis.
						63 hrs.	100.7	86	+	++++	O	O	920	90%	10%	++++	22 cc. H.I.	
115	Aug. 18	Dudley B.‡	Syracuse	Lewis	24	36 hrs.	102.2	136	+++	++++	++++	++++	760	40%	60%	++++	20 cc. H.I.	Paralysis left shoulder‡
						56 hrs.	101.4	100	+++	++++	++++	++++	Cloudy	90%	—	—	20 cc. H.I.	Both lowers.
116	Aug. 28	Harriet M.	Fayetteville	Brand	17	34 hrs.	100.2	160	+++	++++	++++	+++	410	90%		++++	5 cc. H.I.	No paralysis.
						55 hrs.	101	150	+	++++	+	O	Cloudy	60%	40%	++++	5 cc. H.I.	
117	Aug. 12	Barbara B.*	Syracuse	Foreman	2½	36 hrs.	102.6	140	?	++++	++++	+++	210	6%	94%	++++	12 cc. H.I.	Paralysis lat. gaze.
						57 hrs.	101	120	—	++++	+++		Cloudy	90%	—		10 cc. H.I.	No other paralysis.*
118	Aug. 29	Rose S.	Syracuse	Chaffee	17	36 hrs.	100	—	++++	+++	+++	O	180	—	—	++++	18 cc. H.I.	No paralysis.
119	Aug. 7	Robert B.*	Liverpool	Hagen	3	36 hrs.	103	160	?	++++	++++	++++	240	10%	90%	++++	12 cc. H.I.	Paralysis lat. gaze. Transient.*
120	Aug. 1	William B.†	Syracuse	Knopf	9	36 hrs.	100.5	120	+++	++++	++++	++++	510	75%	25%	++++	15 cc. H.I.	Paralysis.†
						56 hrs.	102	—	++	++++	++++		5120	92%	—	—	15 cc. H.I.	
						Left 3d, left 7th, and right shoulder												
121	June 30	Edward J.	Cicero	Winnie	15	38 hrs.	102.6	84	++++	+++	+++	++++	430	10%	90%	++++	15 cc. Pn.	No paralysis.
						62 hrs.	101.4	100	O	++++	O		480	—	—	++++	15 cc. Pn.	
122	Sept. 23	Sylvester G.†	Baldwinsv'le	Sullivan	33	47 hrs.	102.3	134	+++	++++	++++	+	210	—	90%	+	20 cc. H.I.	Paralysis, both lowers.†
123	Aug. 6	*Edward F.*§	*Syracuse*	*Blum*	22	58 hrs.	102	150	++++	++++	+	++	840	90%	10%	++++	15 cc. H.I.	*Paralysis of lowers, unexpected bulbar extension. Died at 90 hours.*§
						77 hrs.	Weakness in lowers beginning						Turbid	—	—	—	15 cc. H.I.	
124	Aug. 25	Franklin N.‡	Syracuse	Coombs	16	52 hrs.	102	142	++++	++++	++++	++++	280	10%	90%	+++	15 cc. H.I.	Paralysis left shoulder.‡
						72 hrs.	Weakness in left shoulder						840	85%	15%	++++	15 cc. H.I.	Weakness, both lowers.
125	Aug. 7	Shirley H.†	Syracuse	Heath	5½	60 hrs.	101.2	134	O	++++	++	++++	240	43%	57%	+++	12 cc. H.I.	Bulbar.†
						62 hrs.	Bulbar involvement, right facial and ext. rectus — appeared moribund but survived											
126	July 27	*Gordon R.*§	*Syracuse*	*Lowry*	20	64 hrs.	101	110	++++	++++	++++	++++	350	80%	20%	++++	15 cc. H.I.	*Extensive paralysis. Exodus at 91 hours.*§
						This case was extremely severe with extensive erythema												

Case 95.—Grant M., aged eighteen years, was seen at sixty hours; 20 cc. of pneumococcic serum was given. Five hours later beginning paralysis of shoulder girdle was noted. Evidently a late case and hardly a frank serum failure. This boy, although distinctly ill, had tried to keep up and about during the first forty-eight hours. An adult sister died of infantile paralysis nine years before.

Case 107.—Alfred M., aged seven years, was seen in a country district, and 10 cc. of human immune serum were given at twenty-four hours. Telephone report on the following morning was of normal temperature and great improvement, and he was not seen at this time by the writer. At seventy-two hours there was temperature of 103° F. and involvement of both uppers with subsequent respiratory death. This is a most distressing case and demonstrates the necessity for careful and frequent observation. Possibly the initial serum amount should have been larger, but by all means this boy should have had a second dose of serum.

Case 110.—Alice S., aged three years, seen 38 miles away, received initial dose of serum at twenty-seven hours. The next day improvement reported and serum not repeated. Death on the third day from upper and respiratory paralysis. This also is a tragic demonstration of the necessity of careful watching and a proper appreciation of the importance and potential fatality in these cases. A second dose should, of course, have been given.

Case 123.—Edward F., aged twenty-two years, was seen in a boarding house at fifty-two hours—definitely a late case. When again seen at seventy-two hours involvement of both lowers had appeared. Temperature was then down and prognosis as to no further extension was considered good. He, however, developed suddenly during the night difficulty in swallowing and died of central respiratory paralysis.

Case 126.—Gordon R., aged twenty years, was seen at sixty-four hours, and was a very severe case. The previous clinical diagnosis was meningitis with extensive erythema suggesting purpura. This was quite evidently a late case with the appearance of paralysis at seventy-six hours.

Of these 8 deaths, 5 were vigorous young adults from sixteen to twenty-two years, and in 4 of them there was definite absence of early bed rest and appropriate care. In 3 of them, serum was given late at fifty-two, sixty-two and sixty-four hours respectively, and just before the appearance of paralysis, obviously advanced cases. In 3 others no second, or repeat, serum was given; in 2 of these, from remote districts, because of telephone reports of apparent improvement and in the third because it was not allowed by excitable and prejudiced parents. The remaining 2 cases are frank failures of serum and without alibi.

There were 25 cases that developed paralysis. Ten were mild and have cleared entirely in the course of six months. Eleven were moderately severe with residual and permanent weakness of one or more extremities. It is of interest to note that of these 25 cases with paralytic involvement only 4 were seen in the first twenty-four-hour period, and also that several might have been benefited by a second administration of serum.

There are listed 93 cases with "no paralysis." This was determined by ordinary neurologic examination directly after the subsidence of the fever and by the absence of any ordinarily detectable disability. In few of these, however, later examination by an efficient orthopedic nurse showed a "weakness of the flexor of the right big toe," or a "slight weakness of the left rectus of the abdomen," but such variations were considered as insignificant and the case considered as nonparalytic. Cases without demonstrable paralysis were allowed up and about in ten days.

Forty-six were seen in the first twenty-four hours. Of these there was one death (Case 6), and one (Case 25) with extensive paralysis. Both of these should have had repeat serum and again well illustrate the absolute necessity of close observation. Three developed mild paralyses. Forty-one recovered, without demonstrable cord involvement.

In contrast, 11 were seen after forty-eight hours. Of these, there were 3 deaths, 3 severely paralyzed, and 2 mildly paralyzed.

Six cases might be considered mild on the clinical evidence and because of the low cell counts. They are listed as follows:

Case 3 at fourteen hours, 20 cells.
Case 4 at fifteen hours, 50 cells.
Case 22 at ten hours, 60 cells.
Case 23 at ten hours, 65 cells.
Case 29 at fifteen hours, 90 cells.
Case 49 at twenty-four hours, 90 cells.

It must be noted that these were all early cases and might have at a later hour shown greater severity. An illustration of this is seen in Case 38, spinal fluid at twenty-four hours showed only 40 cells and serum was not given; at a second puncture, six hours later, there were then 180 cells with a much clearer clinical picture.

Case 57 serves as an illustration of the definite symptomatic picture. It was seen quite out of season on June 8, definitely diagnosed, and treated as pre-paralytic poliomyelitis. The diagnosis was at first received with doubt, because of the unusually early incidence and also the absence of other cases in the community. However, it proved to be one of the first in a subsequent series of 133 and was immediately followed by the appearance of several paralytic cases in the immediate neighborhood.

Nonspecific Serum. Of the 126 cases, 23 were given antipneumococcic serum alone and 8 were given an initial dose of pneumococcic serum and a subsequent dose of human convalescent serum. As far as can be determined from such a small number, there is no great difference in results as compared to the human immune serum. This, to the writer, is very disturbing, as it is nonspecific therapy, and hence in the minds of some might detract from the value of the entire series. No explanation is offered, except that the apparently

beneficial results may be partially due to the phagocytic action of the additional aseptic meningitis produced by this introduction of a foreign serum.

However, it is strongly urged by this observer that the human convalescent serum on the experimental evidence be used. It should also be remembered that the introduction of pneumococcus serum or other nonspecific horse serum is often attended later by severe reactions with urticaria, joint inflammation and acute kidney irritation. In this series, many severe reactions were noted in cases previously sensitized by diphtheria toxin-antitoxin. Such serum sickness does not occur with human immune serum. Therefore, pneumococcic or other horse serum is not to be recommended and was only used in a few cases when immune serum was not immediately available. Also, it has been shown by Flexner and Amos that the intraspinal introduction of horse serum in the experimental animal has seemed to increase the susceptibility of that animal to the coincidentally or subsequently introduced virus.

Serum in Paralytic Stage. The intraspinal administration of serum to the paralyzed cases is considered futile, but sometimes decision in the early paralytic stage is a difficult one. It is often demanded by the parents and the attending physician. Paralysis, well-established, cannot be very much affected by serum, but in the very early hours of paralysis with temperature remaining high, it has been the plan of the writer to examine the spinal fluid and, if the cell-count is above 200, serum is given, this on the premise that if, in the earlier meningeal stage it is of value, then it might also be still of value in neutralizing the virus yet present and possibly active in the surrounding meninges. Serum has been given in 46 such cases, many of which were severe; 18 died and no definite conclusions can be drawn in the others as to whether any benefit was obtained. It seemed occasionally as if symptoms subsided more rapidly without further extension, but, of course, there can be no proof of this and generally serum is not to be recommended in the paralytic stage.

In bulbar types puncture and intraspinal serum are contraindicated. These patients are to be left severely alone and must be kept absolutely quiet. With such quiet they sometimes "slip by" and the added disturbance by puncture and serum might well reverse the balance.

Intravenous Serum. Intravenous administration of serum as recommended by Amos, Draper and others, is difficult of attainment. It necessitates a large amount of serum which is not always available and, in the opinion of the writer, such treatment is not necessary. All the cases in this group were treated by intraspinal administration only.

Comment. It is not held that the answer of the serum problem of poliomyelitis is here presented. Undoubtedly more cases must be accumulated. However, the main argument against such a series

is in the lack of control cases and it is suggested by some that treatment should be only given to the alternate case. In answer, it is again maintained by the writer that such control is quite satisfactorily found in the paralyzed case, the case occurring in the same locality during the same period, which is undiagnosed and untreated in its pre-paralytic stage, and only recognized when paralyzed.

The argument for treatment by lumbar puncture alone cannot be satisfactorily refuted, but the author refuses to take the responsibility of demonstrating its value.

The writer is most appreciative of the fact that a very great and unusual opportunity has been afforded him. It should be noted that for every positive case seen there were many other most interesting conditions to be excluded, making for a most valuable experience. He wishes to especially express his thanks to Commissioners Thomas P. Farmer and Herman G. Weiskotten, of the city of Syracuse, in allowing him to see many of these patients, and he also wishes to express his appreciation of the valued help of Dr. Arthur N. Curtiss, who has been associated with him in this work during the past summer.

Conclusion. It is the belief of the writer that the pre-paralytic stage of poliomyelitis presents a distinct clinical entity; that diagnosis can be, and should be, made early in that stage and that human convalescent serum, administered intraspinally in this period, is of value in preventing paralytic sequelæ, and the earlier in this period, the more successful the result. It is recommended that in any community in which poliomyelitis is occurring, a "Polio" service be established with available convalescent human immune serum and a personnel of diagnosticians, preferably the laboratory man well-experienced as to lumbar punctures, and, if possible, an epidemiologist, a sanitary engineer, an entomologist and a competent administrator. Early diagnosis in the pre-paralytic stage can be made, cases isolated, appropriate treatment given and, what is most important, by such concentrated effort and study, the distinctive mode or modes of spread may be discovered. Then, and not until then, will this treacherous disease be controlled.

CERTAIN NERVOUS COMPLICATIONS FOLLOWING THE USE OF THERAPEUTIC AND PROPHYLACTIC SERA.

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For twenty-five years serum sickness has been a well recognized clinical entity and Boots and Homer Swift[1] but lately have gone so far as to state that most patients receiving considerable amounts of therapeutic serum develop this condition.

The picture of high fever, urticaria and leukopenia, followed by increase of white blood cells, has been for long sufficiently familiar, and, in this country, in 1923, an examination was made of patients with serum sickness in whom acute joint inflammation was a predominant symptom. Such inflamed joints were sometimes swollen and locally raised in temperature having a synovial exudate microscopically indistinguishable from that occurring in joints of patients with rheumatic fever.

The incidence of these intoxications on the skin and mesoderm has thus been recognized and understood but no mention of similar affections of the nervous system has as yet been made in American literature.

In the past two years, however, a number of such cases have come to my attention and, on investigation, it was found that in France also, since 1926 there have been reported[2] postseral neuritides of many peripheral varieties.

I had the opportunity a few years ago to report some cases of angioneurotic edema affecting the brain and meninges in which there occurred focal symptoms from focal dropsies; transient aphasias, transient swellings of the ocular papillæ, transient palsies and transient convulsions syncronizing with urticarial manifestations outside the nervous system. At that time I was ignorant of the nervous complications of serum sickness, some of which at least are the result of the same mechanism as in my earlier material.

Case Reports. In 1 case, to be reported in brief form there were fulminating cerebral symptoms; two had almost identical brachial plexus and circumflex nerve lesions, two others sustained unilateral paralysis of the long thoracic nerves, and 1 case of generalized polyneuritis following antityphoid inoculation will be considered.

Case I.—T. C., aged eleven years, possessed up-to-date parents who prevailed on their medical man to protect their boy against scarlet fever by the use of prophylactic serum which two years ago had just been discovered by the Press. Four days later the boy became severely ill, was covered with urticaria and had a fever of 104° F. Headache was severe from the start; the head was retracted, the abdomen scaphoid and the significance of a constant meningeal cry was made clear by a strongly positive Kernig sign on each side.

On the third day of serum sickness, the patient became aphasic and had a partial right hemiplegia. I saw him two days later when a right homonymous hemianopia was apparent, together with total alexia and jargon aphasia, persistent headaches and the clinical picture of meningeal irritation. There was also bilateral swelling of both optic discs of great severity. Its height could not be measured for no part of the retina could be found in either eye that was not also edematous.

It was this circumstance, however, which enabled a good prognosis to be given, it being apparent that the meninges were the seat of urticarial swelling similar to that seen in the retinæ and in the skin. The cerebrospinal fluid escaped under great pressure and only 14 lymphocytes could be counted per c.mm., a surprising fact in view of the severe meningeal involvement which must have been present.

Our faith in the nature of the mechanism under observation was justified by a gradual recession of symptoms in the following ten days, and four and a half weeks from the beginning of his serum sickness he was reported to me as free of signs and of complaints.

The use of atropin, adrenalin and intravenous glucose may have aided recovery.

In view of our recent Bellevue results in the reduction of intracranial tension by giving large doses of caffein this patient would have been benefited by that drug—however, that is for the future.

CASE II.—H. S., aged eighteen years, the son of one of my colleagues, was seen in February, 1927, three weeks after prophylactic inoculation against scarlet fever, which had been followed by allergic symptoms of great severity. High fever, urticaria, agonizing pains in all the large joints —which were swollen, I was informed, so that their bony form could no longer be made out. There was a numb feeling over the shoulders from the beginning. There was said to be fluid in each affected joint but this must have been hard to determine in view of the great swelling around them. The arms could not be abducted at the shoulders but little was thought of this owing to the severity of the joint pains and the fact that the swelling subsided more slowly in and around the shoulders. However, departure of the shoulder swelling was followed by shoulder atrophy; my examination showed almost total wasting of both deltoid muscles and some wasting of supra- and infrascapular muscles on each side. The right circumflex skin areas was totally without sensation, and the left almost so.

There was complete electrical reaction of degeneration in each deltoid and partial reaction of degeneration in those scapular muscles less stricken. Gradual restoration of strength has taken place during the past year; all movements can now be completed without the use of adventitious or accessory-muscle groups, and total recovery of power is in sight.

CASE III.—F. Z., aged twelve years, was given antitetanic serum on the fourth of July last year following a minor injury to a finger from firecracker explosion. Urticaria, joint pains, and fever followed. The shoulder joints were said to have been swollen but apparently not at all to the same degree as in my other patient. He was brought to me in October as a case of acute poliomyelitis, in that he could not raise the arms at the shoulders from the time of his illness in July. He presented a picture identical in form with my earlier patient but less complete in degree.

There was no evidence of scapular-muscle involvement, but both deltoids were wasted through not totally; there was incomplete reaction of degeneration on both sides and a definite triangle of decreased sensibility in both circumflex areas. In the past six months, there has been steady improvement in symptoms, there is no longer any sensory loss and power is in fair way to complete return.

CASE IV.—R. S., aged fifteen years, ran a spike into his foot and was given antitetanic serum on May 25, 1927, into the left arm. The arm a few days later became swollen and painful and serum sickness followed. The urticaria was extensive but was noticed to be especially severe over the right upper arm and right axilla and right side of trunk. There was no swelling of any joint, though joint pains were intense. After recovery, a deformity of the right scapula was noticed, and he was seen by me at the instance of Dr. Jagger of Flushing on June 9 last. He then had a total paralysis of the right serratus magnus muscle with completely winged scapula and weakness of abduction of the upper arm. I have not learned if any recovery has yet taken place.

CASE V.—J. A.,* aged twenty-one years, fell and sustained a superficial laceration of the scalp. He walked into the "Emergency Room" of a nearby hospital, where the wound was treated and tetanus antitoxin given into the muscles of the left arm.

He had completely dismissed the matter when on the seventh day following the trivial accident, the arm became red, swollen and painful about the site of the infection. A few hours later an erythematous rash appeared over the entire left arm and nowhere else. On the third day subsequent to the appearance of the rash, the right shoulder became painful and a trifle swollen. The pain disappeared at the end of twelve hours. Almost immediately, the left shoulder joint grew painful and continued to annoy him for seven days. The following morning (that is, the morning of the third week from the administration of serum), pain recurred in the right shoulder and persisted for forty-eight hours. There was no further increase of symptoms.

About this time he noticed a weakness of the right upper extremity. The movements of the right upper extremity were awkward. The limb seemed to be "in its own way." The muscles felt too heavy and cumbersome. The difficulty in the execution of movements progressed, and seventy-two hours after he had first become conscious of the weakness he could not raise the right arm to the horizontal position. At the same time, he remarked the winging of the right scapula. (December, 1926, he came to Bellevue Hospital.)

Past history irrelevant save for a gonococcus infection in 1924, complicated by a generalized arthritis, with total recovery.

Physical Status. The boy had an unusually well-developed powerful musculature. There was a complete paralysis of the right serratus magnus with inability to raise the right arm to a complete horizontal position; winging of the scapula was prominent with marked bulging of the infraspinatus. All other muscles were intact, including the right trapezius, upper and lower portions.

The blood Wassermann test was negative.

A radiogram of the right shoulder was negative.

CASE VI.—A. E. T., aged thirty-four years, was seen by my colleague, Dr. George Hyslop, to whose courtesy I am indebted for these notes.

In November, 1924, he was given antityphoid inoculation, the second injection being followed by a severe reaction with high fever and urticaria.

The last dose was given on December 2. The next day he awoke with numbness of the feet, a sensation which spread slowly and steadily upward to the waist. On December 7 it was felt in the ring and little fingers of both hands. He had trouble in focussing objects near him in the midline of vision. At this time there was an incomplete glove-and-stocking anesthesia, and total loss of vibration sense in the legs. The grasps were weak and awkward. Tingling in the hands and feet was painful, and he felt desperately tired. The deep reflexes persisted but were much reduced. For a month the abdominal reflexes could not be obtained.

His symptoms remained for about eight weeks in all, during which time gradual improvement took place.

There are, of course, two possible processes, either of which might produce these conditions. The toxicity of the serum or the urticarial edema of the perineural tissue. Probably both are factors, but I believe the latter mechanism was chiefly responsible for the symptoms of my first cerebral case, and also in the cases of paralysis of

* History kindly procured by my Bellevue Hospital physician, Dr. Aaron Bell.

single long nerves. Here there was clearly palsy by compression and not palsy by destruction of nervous parenchyma.

The site of paralysis coincided with the site of greater incidence of edema; and there was entire absence of nerve involvement other than in the severely affected nerve.

The last case in which polyneuritis followed urticaria consequent to antityphoid inoculation must have been largely toxic in origin, and so in a different causal category.

Conclusion. 1. In view of the occurrences here reported some of great gravity—it would seem wise, before giving serum, to use intravenous injection of sodium carbonate.

2. Immunizing methods which will diminish serum sickness must be devised. In this connection, one remembers how very rare were such conditions during the World War when antitetanic serum was given in hundreds of thousands of doses.

3. When all has been said, however, these are rare accidents, and but a small price to pay for the inestimable benefits obtained by serum therapy in general.

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SEX, AGE AND SEASONAL DISTRIBUTION OF TETANY IN THE ORPHANAGES IN PEKING

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In our metabolic studies[1,2] of the type of tetany that occurs in the orphanages in Peking, it has been shown that this condition cannot be accounted for solely by the low-calcium intake in the diet, and that a deficiency in vitamin D as contained in cod-liver oil or lack of available ultraviolet rays in the sunlight plays an even greater part in bringing about a condition of neuromuscular hyperirritability. Mention was also made of the great prevalence of tetany in these institutions, but exact data were not available. It is the purpose of the present communication to report on the incidence of tetany in two of the orphanges in Peking with respect to sex, age and season.

One of the orphanages studied is situated outside the city, the other inside the city. The bulk of the material was obtained from the institution outside of the city, while the other orphanage supplied data for only 80 girls. As the two orphanages are under the same management and environmental conditions, the data obtained from them were treated together. The boys and girls in the two orphan-

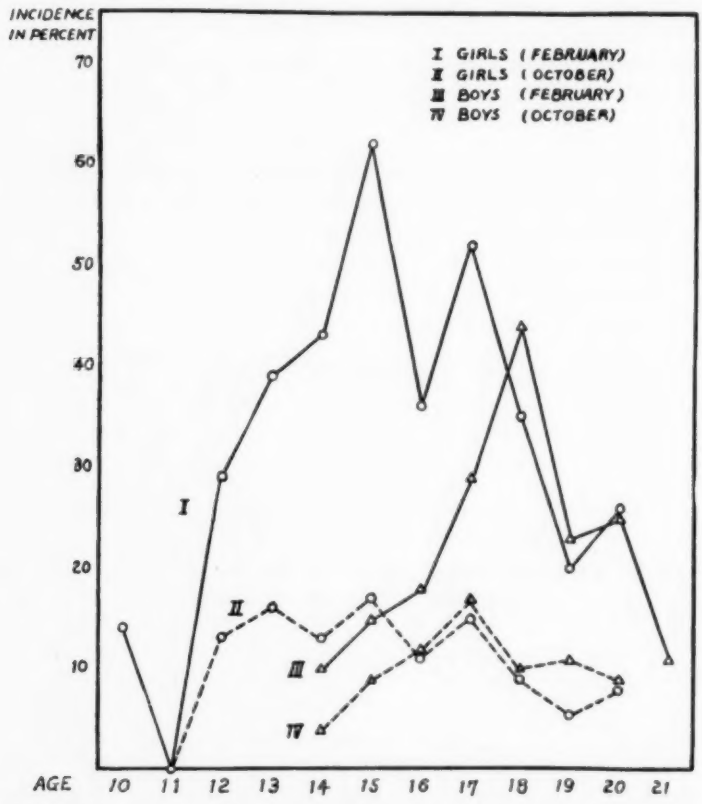

Figure showing sex, age and seasonal variations in the incident of tetany in two orphanges in Peking.

ages were examined in February, 1927, and again in October of the same year. In each case, a history of past and present attacks of spasm of hands and feet was taken, and an attempt was made to elicit Chvostek's sign (facial phenomenon) and Trousseau's sign. Greater emphasis is placed on Chvostek's sign in the diagnosis of tetany, as this sign is found sufficiently reliable and very convenient, especially in dealing with a large number of subjects.

Results. *Sex.* Table I represents the results of examinations made in February, 1927, the late winter season of the year in this

region. The incidence of tetany in females is distinctly higher than that in males. Among the 337 girls examined, 118 (or 35 per cent) showed evidence of various grades of increased neuromuscular irritability, from a positive Chvostek's sign alone to active symptomatic manifestations. However, of the 351 boys examined, only 80 (or 22.8 per cent) exhibited the facial phenomenon and no case of active tetany was observed.

TABLE I.—INCIDENCE OF TETANY ACCORDING TO AGE AND SEX IN FEBRUARY, 1927.

Age.	Male.			Female.		
	Total number examined.	Number showing evidence of tetany.	Percentage affected.	Total number examined.	Number showing evidence of tetany.	Percentage affected.
5	1	0	0	1	0	0
6	1	0	0	..	..	..
7	5	0	0	..	..	..
8	3	0	0	3	0	0
9	4	0	0	6	0	0
10	7	0	0	7	1	14
11	4	0	0	8	0	0
12	8	0	0	7	2	29
13	4	0	0	18	7	39
14	20	2	10	21	9	43
15	27	4	15	29	18	62
16	50	9	18	39	14	36
17	69	20	29	56	29	52
18	57	25	44	63	22	35
19	52	12	23	45	9	20
20	28	7	25	26	7	26
21	9	1	11	4	0	0
22	1	0	0	2	0	0
23	..	..	..	2	0	0
24	1	0	0	..	..	..
All ages	351	80	22.8	337	118	35.0

Age. The age of the subjects examined varied from four to twenty-three years. No cases of tetany were found among the boys before the age of fourteen years. From then on, the incidence of tetany increased with age up to eighteen years when a maximum was reached. After eighteen years, the rate of tetany gradually declined, and after twenty-one years no case was observed, although this age group was small. The onset of tetany in girls was earlier. It began to make its appearance at the age of ten years, and a maximum incidence of 62 per cent was obtained at the age of fifteen years. No cases of tetany were recorded among the girls after the age of twenty years.

Season. If the results obtained in October, the late summer season of the year (Table II), are compared with those in February

(Table I), the reduction in the rate of tetany in the summer is striking. There were only 9.8 per cent of the boys and 10.9 per cent of the girls in whom the facial phenomenon was demonstrable, as contrasted to the corresponding figures of 22.8 and 35.0 per cent obtained in the winter. Not a single case of active tetany occurred either in the male or female group in the summer. The age distribution of tetany was similar in the two seasons. The sex difference in the incidence of tetany, marked in the winter, did not appear to be present in the summer.

TABLE II.—INCIDENCE OF TETANY ACCORDING TO AGE AND SEX IN OCTOBER, 1927.

Age.	Male.			Female.		
	Total number examined.	Number showing evidence of tetany.	Percentage affected.	Total number examined.	Number showing evidence of tetany.	Percentage affected.
4	1	0	0	3	0	0
5	2	0	0	4	0	0
6	3	0	0	3	0	0
7	2	0	0	..	..	..
8	5	0	0	5	0	0
9	3	0	0	8	0	0
10	9	0	0	7	1	14
11	2	0	0	5	0	0
12	8	0	0	15	2	13
13	5	0	0	31	5	16
14	25	1	4	35	5	14
15	34	3	9	35	6	17
16	60	7	12	57	6	11
17	79	13	17	62	9	15
18	75	7	9	55	5	9
19	55	6	11	36	2	6
20	31	3	9	24	2	8
21	5	0	0	5	0	0
22	1	0	0	1	0	0
23	..	..	..	2	0	0
All ages	405	40	9.8	393	43	10.9

Discussion. The great prevalence of tetany in the orphanages concerned suggests the operation of some factor or factors that are related to their diet. Hammond and Hsia[3] have carefully investigated their diet which consists chiefly of millet, wheat and corn meal. It is the same throughout the year, there being no change except occasional substitution of vegetables in season. The fat intake is very low, the protein intake moderately low, and the carbohydrate intake correspondingly high. Calculation from the dietary lists shows that the daily average intake of calcium is approximately 0.004 gm., and that of phosphorus 0.012 gm. per kg. of body weight. Both the calcium and phosphorus intake are far below the minimum

requirements according to the criteria of Shohl and Sato[4] and Ehrström.[5] Undoubtedly, the deficient intake of calcium and phosphorus plays a part in the etiology of tetany, but it does not explain the marked seasonal variation, as the diet remains approximately constant throughout the year. As the incidence of tetany varies inversely with the intensity of the ultraviolet rays of the solar spectrum, a more plausible explanation would be that the ultraviolet rays, being more intense in the summer, are sufficient to make up whatever deficiency there is and thereby decrease the incidence of tetany, but that they become insufficient in the winter, thereby causing a great increase in the rate of tetany. This deficiency in the winter is enhanced by longer hours indoors on account of cold weather.

The relationship between ultraviolet rays and tetany is further established by the therapeutic results achieved with the use of ultraviolet rays in this type of case.[2]

The occurrence of tetany solely in the age groups between fourteen and twenty-one years in the male and between ten and twenty years in the female suggests an association, perhaps more than coincidental between puberty and a tendency to increased neuromuscular irritability. The influence of puberty, if there be any, seems to be even greater on the female than on the male, as the incidence of tetany is higher among the girls than among the boys. Mirvish and Bosman,[6] working on the influence of the internal secretion of the ovary on calcium metabolism, have demonstrated that alcoholic extracts of ovary, liquor folliculi, and corpus luteum reduce the blood calcium in rabbits from 15 to 12 mg. per 100 cc. Similar effects have been observed in human subjects.[7] In the light of this work, may the onset of ovarian function during puberty through association with a lowering of blood calcium offer an explanation of the relatively great incidence of tetany in girls during the age period of thirteen to twenty years, when ovarian activity commences?

Summary. A large group of boys and girls in two orphanages in Peking was examined for evidence of tetany in February and October of 1927. Tetany is more prevalent among girls than boys. It affects the male during the age period of fourteen to twenty-one years, and the female during the age period of ten to twenty years. The incidence is much higher in the winter than in the summer.

Acknowledgment is made to Dr. Chu Han-ying of the Hsiang Shan Orphanage for her kind assistance in this work.

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CARBON DIOXID IN THE TREATMENT OF HYPOSTATIC PULMONARY CONGESTION.

A Preliminary Report.

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Recent developments have emphasized the importance of a more exact consideration of the physiology of respiration with reference to its clinical applications. Particularly has the subject of respiratory stimulation attracted attention. From the earlier neurogenic theory of the respiratory regulation the pendulum has swung to the chemical theory and carbon dioxid is held to be the respiratory hormone. Haldane, in a masterly review of the subject,[1] concluded that "under normal conditions, excluding heavy work, the breathing in man is on an average regulated by the alveolar CO_2 pressure; and a very slight increase or diminution in the CO_2 pressure suffices to cause a very great increase or diminution in breathing." Furthermore, it was established by Hough[2] that the primary response to an increased carbon dioxid content of the respired air is in the depth of inspiration. Twenty-three of 25 subjects showed an early response in this direction and the increase of depth was most marked when attendant upon a decrease in the respiratory rate.

In the present relation the coincident action of carbon dioxid on the cardiovascular system must be given consideration. Concurrent vasomotor and respiratory stimulation were remarked by Kaya and Starling[3] in spinal animals breathing a mixture of 5 per cent carbon dioxid with an excess of oxygen. An elevation of blood pressure, therefore, resulted from this procedure. They concluded that a "moderate increase of carbon dioxid in the blood has no injurious effect on the heart and may possibly, in fact,

improve the functional capacity of the heart muscle." Further studies by Jerusalem and Starling[4] revealed a relaxation of the heart if the carbon dioxid tension of the blood circulating in the coronary system were increased. Of great clinical significance was their determination of a reduced ventricular output at high percentages (12 to 20 per cent of an atmosphere) of carbon dioxid in the coronary circuit. On the other hand, "with moderate tensions of CO_2 (2 to 8 per cent of an atmosphere) the ventricular output increased with increase in CO_2 tensions."

The clinical applications of these facts have been varied. Henderson and Haggard[5] utilized carbon dioxid to combat the respiratory depression of carbon monoxid poisoning. Of the efficacy of this measure there is ample and accumulating evidence. Levi[6] and Cotton[7] had earlier suggested the availability of carbon dioxid in combating surgical shock. Cotton especially stressed the clinical indications of a stimulation of peristalsis by carbon dioxid. Henderson, Haggard and Coburn[8] advocated the use of carbon dioxid in the de-etherization of surgical patients. The following important results were claimed for this treatment: (1) Overventilation washes the anesthetic out of the blood, thereby shortening the duration of the anesthesia; (2) the circulation is stimulated by the hastened venous return from increased respiratory movements; (3) decreased nausea, vomiting and thirst and restoration of intestinal tone are noted. In 1925 Head[9] advocated the use of carbon dioxid inhalations prophylactically and therapeutically in the management of postoperative massive collapse. Scott and Cutler[10] have recently offered substantial evidence for the value of this procedure. Henderson[11] has advocated inhalation of carbon dioxid in the asphyxia of the newborn.

Yet another indication for its use may be found in the hypostatic pulmonary congestion occurring in postoperative surgical cases and in aged and debilitated individuals compelled for one reason or other to maintain a fixed recumbent position. A clearer understanding of the problem may be gained by a consideration of the contribution of normal respiration to the circulation. The inspiratory act induces an appreciable increase in the intrapleural negative pressure, which in turn exerts an active suction on the great venous trunks. The flow of the blood toward the right heart is thus greatly accelerated. According to Macleod,[12] 8 per cent of the total blood is found in the lungs at the height of inspiration as compared with 5 to 7 per cent in expiration. Hence the movement of blood dependent upon respiration is considerable. If the right heart be adequate, the pulmonary circulation is augmented and in turn the output into the systemic circulation rises late in inspiration and continues at a higher level until the expiratory fall of intrapleural negative pressure effects a decrease in the venous inflow. It will be recalled that, while expiration interrupts the flow of blood into the thorax,

it favors the movement of the blood from the lungs into the left heart. Macleod[12] concluded that "it is obvious that increased depth and frequency of the respiratory movements will accelerate the bloodflow and tend to raise the blood pressure." On the other hand, Henderson[13] demonstrated a sharp fall in blood pressure on voluntary hyperpnea. In experimental animals under artificial respiration, succeeding a period of elevated arterial blood pressure, there was observed a shocklike state due to carbon dioxid want. Henderson and Harvey[14] later adduced evidence in proof of the venopressor action of carbon dioxid and stated that acapnia produces circulatory failure by decreasing the venous return to the heart. The available experimental data indicate that increased respiratory rate and depth increase the pulmonary flow and in turn the general circulation; arterial blood pressure thereupon rises. Lastly, a certain tension of carbon dioxid in the blood is optimal for the proper functioning of respiration and circulation.

Hypostatic pulmonary congestion constitutes an important surgical problem in postoperative cases in general, but more especially in the aged and debilitated, as has been previously stated. An important and characteristic group of such serious risks is seen in fracture of the neck of the femur. It is an "old-age fracture." Such a patient is confronted first with the danger of a bronchopneumonia, which if it occurs is almost always fatal, and second the possibility of non-union, the incidence of which is greater than in any other fracture. Hence, the dismay of the physician on being called to treat such a patient is not difficult to explain. It probably lends force to the truth of the statement that "in the interest of their patients they let them die."

The factors of decreased ventilation are accentuated by the fixed recumbency enforced by the plaster of Paris and the debility common to the subject. If the influence of the respiratory movements on the circulation be admitted, clearly any reduction in their rate or depth will impair their contribution to the circulatory efficiency. Passive congestion will occur in the lungs in positions determined by hydrostatic pressure. Dependent congestion may be anticipated or stagnation may occur in local areas of peculiar immobility. Deficient myocardial tone would obviously contribute to the vicious cycle.

Whitman,[15] who advanced the abduction method of treatment now in use, also made provision for the prevention of the bronchopneumonia which so often follows enforced recumbency in the aged. It consists of turning the patient first on the abdomen then on the back. This is of the greatest value in the prevention of a hypostatic congestion of the lungs and should be a routine procedure. It is at best, however, a gravity method, and it is for this reason that the present plan is offered, not to supplant, but rather to act in conjunction with the former method.

The therapeutic indication is for an active respiratory stimulant, and carbon dioxid (with oxygen) furnishes an ideal agent for this purpose. If used as advocated by Henderson and Haggard[5] in asphyxia the concentration of carbon dioxid (5 per cent) will be adequate for respiratory and vasomotor stimulation and yet well within the limits of safety as given by Jerusalem and Starling.[4] Furthermore, the exhibition of the gas itself as the respiratory stimulant will obviate the danger of washing carbon dioxid out of the blood. The deeper respirations induced by the inhalation of carbon dioxid will improve the pulmonary circulation (and in turn the arterial blood pressure will be elevated). The improved pulmonary circulation from increased pulmonary motility may prevent or correct hypostatic congestion of the lungs.

Since 1925 inhalations of 5 per cent carbon dioxid in 95 per cent oxygen have been given to a series of 10 patients with fractures of the neck of the femur admitted to the Orthopedic Service at the State of Wisconsin General Hospital. It should be stated that this group constituted the poorest possible physical risk. All, in whom the gas was used, were very old. Many of them had been transported to the hospital from a distance. As a rule, the fractures had not been reduced as soon as they might have been. In one case an interval of two weeks elapsed between the reception of the fracture and its reduction. Two of the patients died. One, a woman, aged eighty-three years, was received at the hospital the day of the fracture and died four days later, in spite of treatment. The autopsy showed bronchopneumonia. The second fatal case, a woman, aged seventy-six years, had received her fracture fourteen days previous to admission. She had a fever on admission which continued until the time of her death four days later. It is probable that in this case it was unwise to give carbon dioxid because pneumonia was suspected at the time of admission. In 6 of the total of 10 cases hypostatic congestion was established on the basis of decreased vibratory phenomena, suppressed breath sounds and showers of fine crackling râles in the dependent portion of the lungs. As a rule, the physical findings were unaccompanied by serious evidence of respiratory embarrassment, although in 4 instances there was definite dyspnea and cyanosis. In 2 cases the temperature curve suggested an infectious background for the respiratory symptoms and signs. There was dramatic relief of the respiratory distress and cyanosis with coincident clearing of the physical signs of hypostatic pulmonary congestion in 2 of the cases. This group of patients is contrasted with another of 10 cases of fracture of the femur in which carbon dioxid was not used, because it was considered unnecessary. Four of this control group died; 1, very suddenly of pulmonary embolus seven days after admission, 2 of the remaining 3 from bronchopneumonia and the fourth case from late pulmonary embolism.

No rule can be formulated for the dosage of carbon dioxid under these circumstances. Strict attention must be paid to the respiratory response and to the comfort of the patient. As soon as the patient begins to show signs of discomfort or fatigue, the administration of the gas is stopped. Ordinarily a patient will show some distress after two or three minutes. In such cases the mask should be removed and the respiratory rate and depth be permitted to subside. The interval between the inhalations can only be determined by the judgment of the operator. In some cases it is given every hour, in others every three hours, depending on the condition of the patient. Since hypostatic pneumonia is usually a complication of the first week, the advised use of carbon dioxid is especially important during this period. The method should be considered prophylactic rather than curative. The suspicion or actual existence of a pneumonia is an absolute contraindication to its exhibition.

Conclusions. 1. Hypostatic pulmonary congestion may occur in the aged and debilitated as the result of depressed respiratory motility.

2. In such cases as fractures of the femur an apparent relief of early hypostatic pulmonary congestion has resulted from the intermittent inhalation of carbon dioxid.

3. The rate and duration of the administration of carbon dioxid may be controlled by the respiratory response and the comfort of the patient.

4. Differentiation of pulmonary stasis resulting from respiratory depression and that dependent upon right-heart failure must be clearly made, since the use of carbon dioxid inhalations might be strongly contraindicated in the latter circumstance.

5. Overventilation may disseminate an infection from the bronchi or in the alveoli. Hence carbon dioxid inhalations are contraindicated in bronchitis or pneumonia and should also be avoided if such be suspected.

6. On physiologic grounds, a prophylactic value attaches to the use of this measure in all surgical cases meeting the discussed indications, but numbers of cases will be required to establish its value in this relation.

NOTE.—In Current Researches in Anesthesia and Analgesia, 1928, **7**, 187, Sise, Mason and Bogan have suggested the use of carbon dioxide inhalations in the prophylaxis of postoperative pneumonia. Their observations of the improved mobility of the diaphragm as viewed under the fluoroscope are noteworthy. Their results were either equivocal or unfavorable but further studies were advocated before drawing any definite conclusions.

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THE TOXIC PSYCHOSES: AN ANALYSIS OF ONE HUNDRED CASES.

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In view of the fact that many cases of the toxic psychoses are accompanied by uncertainty as to diagnosis, we thought that it would be of considerable value, if we analyzed the records of 100 such cases that have come to our attention, directly or indirectly, in the psychopathic ward of a large general hospital. Toxic mental states are common, and a busy general practitioner observes them daily. We took for study all cases with a diagnosis of toxic psychosis which entered the hospital between 1917 and 1925 except: (*a*) Organic diseases of the brain; (*b*) alcoholics; (*c*) seniles; (*d*) many cases of influenzal psychoses; (*e*) many cases of puerperal psychoses. We have omitted many of the latter two types because they were so numerous that the whole series might have been predominated by them had no discrimination been shown; furthermore, we endeavored to include only those of the puerperal cases which were on a toxic basis, thus excluding those whose mental ill health was due to dementia precox and manic depressive insanity. It is well known that a psychosis peculiar to the puerperium does not occur. As far as richness of material is concerned a similar state of affairs exists, even in this day and generation, in regard to alcoholics. For various reasons the seniles were not considered.

The ages of the patients varied from sixteen to fifty-eight years with the exception of 3, whose ages were thirteen, fourteen and sixty-eight; the average age was thirty-four, that of the females was thirty-one and of the males thirty-nine years. Sixty-six were

females and 34 were males; the number of females exclusive of those suffering from psychoses occurring during the puerperium was 44. The predominance of females is in keeping with the well-known observation that the nervous system in woman is more vulnerable to poisons. As to race, 53 were native born, 31 white and 22 colored; the remainder was made up of a variety of races. The occupation of the individual seemed to have no bearing on the development of the psychosis with the exception of three lead-workers, whose mental ill health was probably traceable to their occupation. The length of time in the hospital was from two to eighty-two days with an average of twenty days. There was a history of previous mental disturbances in 8 cases, 6 of which had had but one previous mental upset and 2 had had two attacks. Three of the 8 were puerperal and in 2 of them the attack occurred following the birth of the first child. Of the puerperal cases, 11 were undoubtedly primipara, with the possible addition of 4 more. One was Para II, one Para III, one Para IV, one Para V and one Para VI.

ETIOLOGIC FACTORS AND RESULTS.

Etiologic factors.	Total No. of cases.	Cured.	Improved.	Unimproved.	Died.
Puerperal	22	8	6	1	7
Influenza	15	12	..	..	3
Pulmonary tuberculosis	7	2	..	..	5
Postoperative	4	2	..	1	1
Nephritis	4	2	..	..	2
Veronal	1	1			
Acetanilid	2	1	1		
Cocaine	1	1			
Lead	3	3			
Hyperthyroidism	2	..	..	1	1
Bronchopneumonia	2	2			
Chorea (Sydenham's)	3	2	..	..	1
Bronchitis	1	..	..	..	1
Bronchiectasis	1	..	..	..	1
Pyonephrosis	1	..	..	..	1
Tetanus	1	1			
Infection of arm	1	1			
Typhoid	1	1			
Mumps	1	1			
Pellagra	1	..	..	..	1
Pleurisy	1	1			
Pelvic abscess	1	..	..	..	1
Carcinoma	3	..	..	..	3
Mitral stenosis	1	1			
Myocardial degeneration	1	..	..	..	1
Septicemia	1	1			
Unknown	18	9	6	2	1

Character of the Psychoses. In analyzing the mental symptoms from which these patients suffered it is easy to understand why so

many of them were at first thought to be examples of dementia precox; it is due to the great frequency of auditory and visual hallucinations occurring in conjunction with delusions of persecution, mental symptoms, which if they occur in young adults, are always suggestive of schizophrenia. In addition, however, 21 of the patients were disoriented as to time and place and were agitated, violent and talkative. Forty-seven had a combination of auditory and visual hallucinations as the chief mental symptoms and 32 had visual and auditory hallucinations and delusions of persecution. Confusion was a common symptom and occurred at least twenty-one times. Depression, homicidal and suicidal tendencies, olfactory hallucinations, delusions of grandeur, in fact the whole run of mental symptoms were present in some.

Duration. The shortest duration with recovery was one day; the longest was one and a half years; the average duration in the cases with recovery was six weeks. Thirty patients had had fever in the course of the illness, although a great many more, such as those occurring after influenza, had had an elevation of temperature during the acute illness.

Heredity. While the records were frequently incomplete about this important phase of the history, in only 4 was there a distinct history of mental disease or epilepsy in the family. This is almost too good to be true, because the histories of 100 supposedly normal people would show a larger number of mental diseases in their respective families than does our series.

Laboratory Findings. The urine was examined in 92 of the cases and showed albumin in 21 and casts in 11. A blood Wassermann was taken in 84 and was positive in 10, but in our opinion none of these cases were general paresis, although syphilis may have played a rôle in the production of the mental aberration. Blood chemistry studies were carried out in 40 of the group and showed practically no deviation from the normal, except that 4 had a blood-sugar estimation from 150 to 180. The spinal fluid was studied in 35 cases, 3 of which had positive Wassermanns with the cholesterinized antigen alone and none had a positive reaction with the Noguchi antigen. The colloidal-gold curve was negative in all in which the fluid was examined with the exception of 2, in both of which it was of the so-called syphilitic type and in both of these the Wassermann was negative. Complete blood counts were recorded in only 8, 7 of which had a leukocytosis ranging from 14 to 40 thousand; 1 case showed basophilic degeneration.

Outcome. Fifty-three were discharged as recovered; 13 improved; 4 unimproved; 30 died. The etiologic factors in the 4 unimproved cases were exopthalmic goiter, postoperative, pregnancy and the fourth, unknown. The largest number of deaths, (7) occurred among the puerperal psychoses. Five deaths were due to tuberculosis and 3 to carcinoma. Autopsies were performed on 7

of the subjects, but in only 2 of these was the brain examined; in 1 case the brain presented a cerebral edema and in the other showed marked congestion and neuronophagia.

Follow-up Investigation. Follow-up visits were made in 53 instances, in 10 of which, however, no information about the patients could be obtained, so that completed reports number 43.

The last patient included in our series was discharged from the hospital in December, 1925, so that all cases have been disposed of practically one year or more, and a large percentage returned home a number of years ago. Thirty-six of the patients have remained mentally well since their stay in the hospital and have resumed their former occupations. One of the 36, however, died four years after discharge, but his psychic health was unimpaired until the time of his death. He was a printer, and the etiologic factor was probably lead; he dropped dead while working at his machine, so that his death was probably of cardiac origin.

Five of the patients whom we investigated since their return home had second attacks. The first of this group was an Italian male who had a postinfluenzal psychosis and was discharged cured, although it is proper to say that he could not speak English and his supposed cure may have been due to the fact that he became quiet, whereas formerly he had been disturbed. In any event, after his discharge from the hospital he became worse and committed suicide six months later. Another patient, a woman, aged twenty-four years, had a recurrence of her psychosis from which she also recovered and at the present time is normal mentally. This patient has pulmonary tuberculosis. The third was a male, aged fifty-five years, who was discharged as improved but never entirely regained his health. He was discharged against advice and died six months afterward. He had chronic bronchitis and asthma. The fourth case was a white woman, aged fifty years, whose first attack of mental illness lasted only eleven days and the etiologic factor was thought to be mitral stenosis. She had a second attack during which she was committed to the mental department at Byberry and subsequently was paroled from that institution. The fifth patient who had a recurrence was a white woman, aged twenty-five years, who became mentally ill six weeks after delivery and recovered rather quickly. Subsequently, she was committed to the Pennsylvania Hospital for Mental Diseases and again recovered her mental health. It is worthy of note that this woman later died of pulmonary tuberculosis; the frequent occurrence of intrathoracic disease is significant. Two of the cases about which good follow-up records were obtained remained broken mentally. Of the 8 patients who had had previous mental upsets only 4 could be located. Three of them have remained mentally well until the present time; the fourth is a woman who has pulmonary tuberculosis and she has had a third attack.

Discussion. As mentioned before, we have omitted alcoholics and seniles and many cases of influenzal and puerperal psychoses. Some conditions which frequently are complicated by mental symptoms are missing from our list of etiologic factors, such, for example, as primary anemia and diabetes mellitus; their absence is probably due to the fact that the records of those patients are usually not filed under the heading "toxic psychosis." Furthermore, a great many patients who have mild mental symptoms which occur in the course of kidney, liver, cardiac and pulmonary disease have not been included, as they are not customarily transferred to the psychopathic department as long as they do not upset the ward to which they have been assigned. We are fully aware of the frequency with which mental symptoms occur in all of the foregoing conditions.

The history of the onset in a great many of our 100 cases was sudden; quite a few of the records read "Patient picked up by the police and brought to the hospital." The abruptness of onset should be enough to put the diagnostician on his guard as to the possibility of a toxic psychosis, especially if paresis and other forms of organic cerebral disease can be excluded. A toxic psychosis may simulate very closely dementia precox and it is here that the differential diagnosis must be very carefully considered. The family histories in instances of patients who have dementia precox usually reveal nervous or mental disease in some form, whereas, as we have mentioned above, very few of our cases had bad mental heredity. Hallucinations and delusions of persecution are common to both forms of mental disease. The patient with a toxic psychosis is usually more talkative, more excitable, and the symptoms in general are more bizarre than those of dementia precox. Many individuals, psychotic from a toxemia, early become partly disoriented, a symptom which does not so quickly occur in an adolescent psychosis. To differentiate the two conditions it becomes evident, therefore, that a most careful and exhaustive physical examination is necessary, especially if a fever or signs of toxemia are present. The physician to whose care the treatment of any group of patients with mental symptoms falls should be fully aware of the possibilities, and if not equipped himself to ferret out the cause, he should call into consultation an internist. Every psychiatrist, however, should have a good fundamental training in internal medicine, without which he is frequently lost in a sea of uncertainty. It is needless to say that psychoanalysis will not aid in the diagnosis of the group.

The toxic factor in the psychoses is not confined to the group of cases which we have discussed, but is a very important one in all mental diseases, especially dementia precox, although the exact nature of the toxemia is usually elusive.

The prognosis, generally speaking, in an ordinary toxic case is good and the list of recoveries is large. The number of deaths, 30 in our

series, attests to the severity of the underlying toxic factor, some of which render the prognosis hopeless from the start.

Summary. The analysis of the cases admitted to the observation ward of the psychiatric service of the Philadelphia General Hospital reveals that many of these patients suffer from various forms of toxemias and physical defects which give rise to psychiatric reactions of a toxic nature. The frequency of such reactions makes it imperative that each mental case be studied most thoroughly from the history and physical standpoint to determine if such factors exist. The range of etiologic factors is wide.

REVIEWS.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY (Volume III). By D. THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.P.H. (CAMB.), Hon. Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London and R. THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 316; 57 illustrative plates. Baltimore: The Williams & Wilkins Company, 1927.

VOLUME III of these Annals is entirely devoted to the Streptococcus Group. It is an attempt to differentiate graphically and otherwise between the large numbers of varieties of streptococci. It is an effort also to compile a reference work of value to the research worker, an attempt to present to him a more or less organized mass of information on the work which has been done on the subject up to the present time.

There is presented a full account of the bacteriologic researches describing the streptococci—as to their morphology, cultivation, staining, cultural characteristics on various media, technique for isolation, biochemical reactions, soluble products, virulence, immunity reactions, filtrates, mutations and pleomorphism. There is also included a historic review of streptococci described in the past, various classifications including that by the use of Crowe's differential medium, and a complete bibliography. A most valuable aid to the research worker is presented in 57 full-page illustrative plates which contain 385 very exceptional photomicrographs. Five of these plates are in color.

The Volume is to be recommended to the research worker; it will undoubtedly help him to see clearly the problem that is before him and enable him better to avoid the mistakes which have been made in the past. W. K.

IDIOSYNCRASIES. By SIR HUMPHREY ROLLESTON, BART., K.C.B., F.R.C.P. Pp. 119. London: Kegan Paul, Trench, Trubner & Co., Ltd., Broadway House, Carter Lane, E. C., 1927. Price, 2/6.

THIS handy little volume, No. 8 in the Medical Series of Psyche Miniatures, is an interesting disquisition by an able author upon

the current opinions on the subject of idiosyncrasies, "the abnormal reactions in an otherwise normal person, which may be either, on the one hand, greatly exaggerated or, on the other hand, greatly diminished," as finding their expression clinically in the diseases in which hypersensitiveness is a proven or a suspected factor.

R. K.

ANNALS OF THE PICKETT-THOMSON RESEARCH LABORATORY (VOL. IV, PART I). By DAVID THOMSON, O.B.E., M.B., CH.B. (EDIN.), D.PH. (CAMB.), Honorary Director, Pickett-Thomson Research Laboratory, St. Paul's Hospital, London; and ROBERT THOMSON, M.B., CH.B. (EDIN.), Pathologist to the Pickett-Thomson Research Laboratory. Pp. 250; 49 photographs. Baltimore: The Williams & Wilkins Company, 1928.

VOLUME IV of these *Annals*, devoted to the pathogenic streptococci, is presented in two parts. Each part appears in a separate volume and includes four monographs. The streptococci are examined in relation to the different diseases with which they can be identified, and a separate monograph compiled on each disease. Part I includes the four completed monographs:

1. The Rôle of the Streptococci in Rheumatic Fever.
2. The Rôle of the Streptococci in Chorea.
3. The Rôle of the Streptococci in Erythema Nodosum.
4. The Rôle of the Streptococci in Carditis.

The streptococci isolated from cases of rheumatic fever by Small, Birkhaug, Barlow and others are presented to the research worker in 49 remarkably clear photographs, illustrating certain of their cultural characteristics and morphology.

This volume includes only the first four of the monographs dealing with pathogenic streptococci, a subject which will be completed in the further volumes now in preparation, to wit: Vol. IV (Part II), Vol. V, Vol. VI and Vol. VII. This volume is, therefore, especially important as a unit in the proposed comprehensive study of pathogenic streptococci which will undoubtedly aid materially in identifying the great majority of the many varieties of streptococci.

W. K.

CONVALESCENCE. HISTORICAL AND PRACTICAL. By JOHN BRYANT, M.D. Pp. 269; 94 illustrations. New York: The Sturgis Fund of the Burke Foundation, 1927.

THIS work contains a miscellaneous collection of chapters which deal primarily with the subject of convalescence. The book, however, is not in any sense a textbook or handbook on the subject. The first fifty pages are devoted to a chronologic review of the subject and then follow chapters on the Burke Relief Foundation,

Cleveland Hospital and Health Survey and Houses of Rest in Russia. Part II is chiefly concerned with the convalescent work carried on in the United States Army and Part III is a progress report from 1920–1927. It is not a book for the student of medicine or the practitioner, unless he wishes specialized information concerning convalescence. O. P.

TOTAL X FOTOS. By DR. DENIS MULDER, Dir. Med. Rad. Instit. Pp. 57; 38 illustrations. Bandoeng: G. C. T. Van Dorp & Co., 1927. Price, $1.80.

IN this short monograph, the author has attempted to outline advantages for making radiograms of a part or the entire body at 10 meters. In most roentgen laboratories, films are readily made at a target film distance of 2 meters. At that distance the amount of distortion is approximately 4 per cent. For all practical medical purposes, the 2 meter seems adequate. Increasing the target film distance to 10 meters in the examination of patients is not practical, because of the time, of the exposure, movement of patient, and so forth. The value of roentgenographs of paintings, statuettes, wood carvings, and so forth, are illustrated and discussed. E. P.

BLOOD AND URINE CHEMISTRY. By R. B. H. GRADWOHL, Director of the Gradwohl Laboratories and IDA E. GRADWOHL, Instructor in the Gradwohl School of Laboratory Technic. Pp. 542; 117 illustrations. St. Louis: C. V. Mosby Company, 1928. Price, $10.00.

APPROXIMATELY half of the book is devoted to a description of those methods for chemical analysis of blood and urine that are used in the laboratory of a general hospital. The latter part of the book is given over to the interpretation and application of chemical methods to disease, particularly nephritis, diabetes and gout. The final chapter is devoted to basal metabolism.

The author quotes extensively from the literature, in fact a considerable part of the book is transcribed from other authors.

The book may be useful in a hospital laboratory but one would hardly consult it for authoritative statements because apparently the author, in his conservatism, has failed to give more recent methods and to state the more recent views on the subjects that he treats. The text is too long for a simple technique book and not sufficiently judicial for a treatise. L. J.

EXERCITATIO ANATOMICA DE MOTU CORDIS ET SANGUINIS IN ANIMALIBUS. By WILLIAM HARVEY, M.D. Tercentennial Edition. With an English Translation and Annotations by CHAUNCEY D. LEAKE, Professor of Pharmacology, University of California. Pp. 154; 10 illustrations. Springfield, Illinois: Charles C. Thomas, 1928. Price, $3.50.

AMONG the more permanent reminders of the Harvey Tercentenary—an anniversary worthily celebrated in many countries and in many ways—none is more satisfactory than Leake's Tercentennial Edition, which with Keynes' Nonesuch edition, and Lier's publication, will probably remain the last word in Harvey editions for some time to come. From the new and vigorous Thomas press, this volume presents a novel format on excellent paper with the pleasing Caslon old style type.

Following a facsimile of the original Latin edition of 1628 is the author's translation, the third to be done into current English idiom. This is admittedly free and is designed to replace the somewhat stilted phraseology of Willis' standard English version, which, however, has been used as a "pony" guide. Occasional illuminating but not oppressive footnotes have been inserted. A comparison of the two translations soon convinces one that Doctor Leake has succeeded in his object of making Harvey's treatise more attractive to modern readers without loss of accuracy. A translator's postscript, a chronology of Harvey's life, and a rather scanty index conclude the volume. E. K.

MODERN X-RAY TECHNIC. By ED. C. JERMAN. Pp. 260; 110 illustrations and charts. St. Paul, Minneapolis: Bruce Publishing Company, 1928. Price, $5.50.

THIS book outlines simply some of the principles involved in roentgenography. The author has arranged at the end of some chapters a catechism which should greatly facilitate students of the branch of medicine and technicians. There are several conclusions drawn by the author that cannot be accepted without comment.

1. Registry of Technicians. It is questionable whether this registry should be supported by roentgenologists.

2. The Curved Bucky Grid. The late Dr. Caldwell was one of the early investigators of the method described for reducing the secondary radiations by a grid. He recommended a curved grid. The curved Bucky grid has some advantages that are not possessed by the flat Bucky, but the latter has a greater number of advantages over the curved, and is probably more universally used.

Except for some of the special examinations, the author has considered most of the routine examinations. The illustrations of the technique and the resulting roentgenogram are well illustrated. I have no doubt that this book will serve a useful purpose in supplying the need of students and technicians interested in roentgenography. E. P.

PROBLEMS IN SURGERY. By GEORGE W. CRILE, M.D. Pp. 171; 49 illustrations. Philadelphia: W. B. Saunders Company, 1928. Price,$4.00.

THE reader needs no introduction to the author of this little book. It is not a textbook in any sense of the word. It is rather a treatise on six different subjects, in every one of which the author is qualified to express an opinion. His first talk on management of acute infections is concise and to the point. The essay on the bad-risk patient lies well within the field that this writer has so extensively explored. The chapter on diagnostic and operative clinics is an excellent one. The Reviewer recommends the reading of this work by every one interested in better surgical results. E. E.

NEUROLOGICAL EXAMINATION. By CHARLES A. MCKENDREE, A.B., M.D. Associate, Department of Neurology, College of Physicians and Surgeons, Columbia University; Associate Physician, Neurological Institute, New York. Pp. 280; 88 illustrations. Philadelphia and London: W. B. Saunders Company, 1928. Price, $3.25.

THE study of the signs and syndromes shows lucid and inclusive treatment. A generous allotment of space for examination of the cranial nerves gives another valuable section.

As the reviewer sees it, the weakness of the book lies in the section on Mental Status, made distressingly short—12 pages out of 280—and at that, more than half of the subject matter is written by a psychologist, who further wastes space by padding her theme with historic data. N. Y.

DIABETIC MANUAL FOR PATIENTS. By DR. HENRY J. JOHN. Director of the Diabetic Department and Laboratories of the Cleveland Clinic. Pp. 202; 42 illustrations. St. Louis: The C. V. Mosby Company, 1928. Price, $2.00.

THIS book is another of a rather frequent type written for the diabetic patient. The author discusses among other things those

conditions that influence the course of the disease, the rôle of blood and urine sugar, insulin treatment and dietetics. At the end of the book there are the usual tables of food values and recipes. The subject is presented in a very lucid style that will permit the laity to obtain a knowledge of this condition. L. J.

A Short History of Medicine. By Charles Singer, M.A. M.D., D.Litt., Fellow of the Royal College of Physicians of London, Lecturer on the History of Medicine in the University of London. Pp. 368; 142 illustrations. New York: Oxford University Press, American Branch, 1928. Price, $3.00.

Like all the author's medicohistorical writings, this book is fresh, thoughtful, interesting and correspondingly valuable. Even though it is a discussion of the principles of medicine from the historical standpoint more than a history of medicine in the traditional sense, it is a valuable adjuvant to such a history for the medical reader. It is addressed chiefly, however, to the intelligent layman. For him, more concerned with principles, sufficiently elucidated with cognate explanations, than with a detailing of all the strictly medicohistorical facts, it is even more valuable than a conventional history, with the added recommendation of moderate cost.

Following the chronologic approach, the author discusses in turn the medicine of Greece and its heirs, the Middle Ages, the Renaissance, the period of Consolidation (1700 to 1825) and the period of Scientific Subdivision (from 1825 on), to which last almost half the book is devoted. Emphasis is placed on the development of ideas rather than on the lives of those enunciating them, while the author's individual ideas, too, are often apparent. A vitalist in company with Aristotle, Harvey, Hunter, Claude Bernard, Joh. Müller and Virchow, he believes that "there is a principle in living things that cannot be expressed in physical or chemical terms." Recognizing that this is not a useful point of view in modern medical research, nevertheless he sees no reason for abandoning it as a point of view that makes existence intelligible. Certainly all must admit that mechanism, while contributing many useful scientific explanations, has thus far totally failed to explain life.

Together with a rational survey of an extensive field, the author has combined in small space a surprisingly large number of interesting historical facts and illustrations, many not easily available elsewhere. We heartily recommend the book to thoughtful medico and layman alike. E. K.

BOOKS RECEIVED.

NEW BOOKS.

*Report on Mussel Purification.** By R. W. DODGSON, M.D. (LOND.), M.R.C.P., (LOND.), M.R.C.S. (ENG.). Pp. 498; illustrated. London: His Majesty's Stationery Office, 1929. Price, £1 1s.

*Spinal Anesthesia.** By CHARLES H. EVANS, M.D. Pp. 203; 41 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $5.50.

*Harvey Lectures, 1927–1928.** Pp. 280; illustrated. Baltimore: Williams & Wilkins Company, 1929. Price, $4.00.

*Malaria Problems.** By FREDERICK L. HOFFMAN, LL.D. Pp. 207. New York: Prudential Insurance Company, 1928.

*Thyroxine.** By EDWARD C. KENDALL, M.S., PH.D., D.SC. Pp. 265; 38 illustrations. New York: The Chemical Catalogue Company, 1929. Price, $5.50.

*Clinical Physiology.** By ROBERT JOHN STEWART MCDOWALL, D.SC., M.B., F.R.C.P. (EDIN.). Pp. 383; 4 illustrations. Philadelphia: D. Appleton & Co., 1928.

*Textbook of Clinical Neurology.** By M. NEUSTAEDTER, M.D., PH.D. Pp. 602; 228 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $6.00.

*The Story of Modern Preventive Medicine.** By SIR ARTHUR NEWSHOLME, K.C.B., M.D., F.R.C.P. Pp. 295; 9 illustrations. Baltimore: Williams & Wilkins Company, 1929.

*Medical and Allied Topics in Latin Poetry.** By HEINRICH OPPENHEIMER, D.LIT., LL.D., PH.D. (LOND.), M.D. (HEIDELBERG), M.R.C.P. (LOND.). Pp. 445. London: John Bale, Sons and Danielsson, Ltd., 1929. Price, 30s.

Surgical Clinics of North America. (Mayo Clinic Number) February, 1929. Pp. 247; 141 illustrations. Philadelphia: W. B. Saunders Company, 1929.

*Spasmophilia.** By EDWARD C. WRIGHTSMAN, M.D. Pp. 155; 24 illustrations. Boston: Richard G. Badger, 1929.

NEW EDITIONS.

*An Index of Differential Diagnosis of Main Symptoms.** Edited by HERBERT FRENCH, C.B.E. (MILITARY), M.A., M.D. (OXON.), F.R.C.P. (LOND.). Fourth edition. Pp. 1171; 701 illustrations. New York: William Wood & Co., 1929. Price, $18.00.

The A B C of Hydrogen Ion Control. Fifth edition. Pp. 132; illustrated. Baltimore: La Motte Chemical Products Company, 1929.

A simple description of the colorimetric method of PH determination with its application to various commercial processes.

* Reviews followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Can the Gall Bladder Empty Through Duodenal Biliary Drainage? Is the Gall Bladder the Source of "B" Bile? A Cholecystographic Study of Biliary Drainage.—In 1917, the late Dr. Meltzer published in the AMERICAN JOURNAL OF MEDICAL SCIENCES an article upon disturbances of the law of contrary innervation in diseases of the bile duct and gall bladder, inserting at the end of his paper a foot note which read as follows: "In experiments with magnesium sulphate I observed that the local application of a 25 per cent solution of that salt upon the mucosa causes a completely local relaxation of the intestinal wall. It does not exert such an effect when the salt is administered by the mouth. The duodenal tube, however, apparently has reached an efficient practical stage. I therefore make the suggestion to test in jaundice and biliary colic the local application of 25 per cent solution of magnesium sulphate by means of the duodenal tube." This paragraph has occasioned a great deal of controversy in medicine in the past few years because of the clinical application of this suggestion of Dr. Meltzer, LYON (*Arch. Int. Med.*, 1929, **43**, 147) was the first to grasp the significance of this statement and through his earnest efforts the method suggested to drain the gall bladder has been extremely widely used throughout this country and Europe. However, there has been considerable controversy and discussion as to the merits and the value of this particular clinical procedure. In order, as the author says, to settle the question definitely, a study was made in association with Dr. Cole on the cholecystographic evidence of biliary drainage. At the same time a chemical study was made of the bile drained from the gall bladder by means of the duodenal tube. Before starting the account of his results, Lyon discusses briefly the surgical, experimental, cholecystographic and chemical proof that has been brought forth to show that the gall bladder contracts by its own intrinsic musculature and that secretory pressure, abdominal pressure and action of the sphincter play no important part whatever in this physiologic act of

emptying the viscus. In the present study 19 patients were selected for study, the idea being to make roentgenograms of the gall bladder sixteen or eighteen hours after the ingestion of tetraiodophenolphthalein. These people had or were presumed to have gall-bladder disease. Each one took a dinner rich in fat at 6.30 P.M. Three hours later they started the ingestion of the dye, a total of 3.5 gm. being given them. At 8 o'clock the next morning, the stomach being empty, a tube was passed, controlling the location of the bulb with the Roentgen ray after taking the gall-bladder picture. Thirty-three per cent magnesium sulphate, and in some cases 10 per cent peptone or 30 cc. olive oil, was injected through the tube. The bile was subsequently drawn through the tube and tested for iodin. Several hours later, after a fat rich meal, they were again examined by the Roentgen ray. Results: Four patients were discarded. The remaining 15 were divided into two groups. In Group I there were 8 patients who showed in practically every case a complete reduction in the size of the shadow of the gall bladder and in each patient there was a marked variation in the iodin content of the "B" bile and "C" bile. The "B" bile contained from 3.4 mg. of iodin per 100 cc. of blood to 9.6 mg., whereas the "C" bile varied between 0.42 and 3.2 mg. In the remaining 7 patients the results were not so satisfactory, due to the failure of the dye to show the gall bladder, inability of the patient to take the capsule satisfactorily, or for some other reason. While the reduction in the size of the shadow in these cases was not satisfactory, nevertheless, the iodin content of "B" bile was infinitely greater than the "C" bile. The author concludes as a result of the study that the question of genesis of "B" bile and "C" bile is definitely settled; that the gall bladder empties its contents by means of its intrinsic musculature; that good specimens of bile may be obtained by intraduodenal stimulation of magnesium sulphate; that specimens of gall-bladder bile are therefore procurable for chemic and bacteriologic study; and that we can now turn our attention to the investigation of the value of duodenal biliary drainage as an adjunct therapeutic agent in various problem diseases. The author has covered his subject well and has presented his work satisfactorily, so that in truth there can be no question as to the physiologic response of the gall bladder to intraduodenal stimulation. The only question of a controversial nature that he has not answered is: why gall-bladder drainage for the purpose of treatment, not diagnosis, when a fat-rich meal apparently may cause exactly the same sequence of events as the magnesium sulphate lavage?

Myocardial Disease and its Gastric Masquerades.—RIESMAN (*J. Am. Med. Assn.*, 1928, **91**, 1521) presents some very timely words of warning to the gastroenterologists in reference to the frequency with which gastric symptoms obscure the true underlying pathologic process of disease. These observations are particularly pertinent when one remembers the tendency of the man limiting himself to a small specialty to neglect a thorough survey of the patient. Eight brief case reports are given, all of which are used for examples to illustrate the frequency with which cardiac disease produces evidence of gastric dysfunction. The obvious way of preventing these diagnostic errors, which might prove very serious, is to make a thorough examination of the patient, accepting neither his diagnosis nor the diagnosis of others as to his condition.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY, SCHOOL OF MEDICINE AND ASSOCIATE PROFESSOR OF SURGERY, GRADUATE SCHOOL OF MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Treatment of Vertebral Tuberculosis by the Spine Fusion Operation.—Hibbs and Risser (*J. Bone and Joint Surg.*, 1928, **10**, 805) states that the operative mortality was only nine-tenths of 1 per cent, all of whom were poor risks. It seems undoubtedly true that the results of this series would have been better if the cases had been operated upon early. Analysis of these facts shows that mortality and lowered resistance to tuberculosis is directly proportionate to the number of local manifestations of the disease. The percentage of deaths in the group having two spinal foci was 36, as contrasted with 26 in the entire series. Fifty per cent of the series complicated by hip-joint tuberculosis had a fatal termination and all of these who had tuberculous peritonitis or nephritis died. In that group, in which Nature had made an attempt at elimination of motion by an area of natural fusion of posterior vertebral elements, there were only 13 per cent of deaths and not one was due to tuberculous peritonitis. Thus it would seem that early elimination of motion in all diseased joints would increase the patient's resistance. Any treatment to be most effective in vertebral tuberculosis must be applicable to children, as most cases occur in children. Fusion takes place more rapidly in them and their recuperative powers are better. The enforced inactivity over long periods of time, so commonly used in the treatment of this disease in children is detrimental to their physical and psychologic development. Furthermore, there is no justification in the hope that all diseased joints become fused by such means. The diagnosis of tuberculosis of the spine should be possible very early, by Roentgen ray and physical examination. The hope of improving the results in the future depends upon the education of the medical profession in the methods of early diagnosis and upon their urging immediate operation.

The Blood Supply to the Appendix.—Koster and Weintrob (*Arch. Surg.*, 1928, **17**, 677) state that the macroscopic observations on the blood supply to the normal appendix show that the appendicular arterial tree is remarkably constant in its architecture. The definite determination of the supply into two layers, the richer of which is the deeper and the absences of a distinct blood supply to the mucosa are undoubtedly of physiologic importance. Attention is again drawn to the remarkable corkscrew and spiral character of the appendicular branches of the second, third and subsequent orders. From analogy with other organs

in which this type of vessel is found; for example, the uterus, intestine, urinary bladder, and so forth, this tortuosity speaks for a structure which is constantly changing in shape and in caliber. The next striking point about the blood supply is its richness and profuse anastomosis. This again is analogous to the condition found in organs subject to vascular obliteration, for example, the heart. The number of fat vessels found in the mesoappendix, seems to be out of proportion to that necessary to nourish a similar amount of fat and the close parallelism between the prominence of these vessels and the extent of the inflammatory process in the appendix suggests that these vessels play a compensatory rôle.

Diverticulosis of the Appendix and Pseudomyxoma Peritonei.—CHOYCE, RANDALL and GARDHAM (*Brit. J. Surg.*, 1928, **16**, 62) note that the main interest of diverticulosis of the appendix lies in the relation of the condition to pseudomyxoma of the peritoneum. Diverticulosis of the appendix appears to be a condition of only moderate rarity. It can be said with certainty that diverticulosis of the appendix is a much less rare condition than pseudomyxoma peritonei. On the other hand, those cases of pseudomyxoma peritonei which have originated from the appendix have been shown in nearly all cases in which the appendix has been fully investigated, to be associated with diverticula. It appears then that diverticula of the appendix frequently, but not necessarily, lead to a pseudomyxoma of the peritoneum. It remains to decide the additional factor which must be present for a diverticulum to lead to pseudomyxoma peritonei. The presence in many of the recorded early cases of an omental mass in the region of the pseudomyxomatous appendix and the fact that pseudomyxomatous nodules in the omentum have come to be regarded as a characteristic sign in the early stages of the disease, suggest together that the omentum is closely connected with the production of pseudomyxoma peritonei.

An Experimental Study of Muscle Atrophy.—LIPPMAN and SELIG (*Surg. Gynec. and Obst.*, 1928, **47**, 512) say that the muscle atrophy that follows the fixation of a limb is small in degree and is not appreciable before the lapse of at least a month. It is not comparable to the atrophy caused by nerve section, tenotomy and arthritis either as regard its onset or the proportions that obtain in these conditions. The atrophies that follow tenotomy, nerve section and arthritis are extremely rapid in onset and the progression is almost equally as brisk in all these conditions. The muscle atrophies that follow tenotomy and nerve section are due to cessation of muscle formation and are therefore disuse atrophies. The atrophies that follow experimental arthritis are preceded by muscle relaxation, "muscle collapse" and the subsequent course is the same as that which obtains following tenotomy and nerve section. It is, therefore, reasonable to conclude that arthritic atrophy is also a disuse atrophy. The muscle disuse, however, is not caused by voluntary immobilization or external fixation, but is due to the "muscle collapse." Hence the theoretical and experimental evidence leads to the inference that although arthrogenic atrophy must be considered a disuse atrophy, it is not due to immobilization but it is caused by a reflex mechanism.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY.

Suprarenal Transplantation and Organotherapy in Addison's Disease.—Fairly satisfactory results in the treatment of Addison's disease having been reported by a number of workers who administered large daily doses of fresh whole suprarenal gland, ERICH LESCHKE (*Med. Klin.*, 1928, **24**, 1268) undertook to employ this treatment in a girl, aged twenty-eight years, suffering from a severe grade of Addison's disease presumably due to tuberculosis. After the treatment had been continued for four and a half months without any benefit, the patient had lost so much ground that the prognosis seemed hopeless. At this time the opportunity arose to obtain the greater part of a normal suprarenal gland from a patient at operation. This was implanted directly at the time of operation into a pocket in the abdominal muscles of the girl with Addison's disease. The results were extraordinary. The patient regained her appetite, her strength returned, the blood pressure rose from a level of 85 mm. to between 110 and 125, blood sugar became normal, and the skin pigmentation diminished rapidly. Menstruation which had long been absent appeared eight days after transplantation and has since worked regularly. There was also a marked growth of axillary and pubic hair. Shortly after transplantation it became impossible to continue the administration of fresh suprarenal glands as these could not be obtained, but treatment was continued with extract of the whole gland and injections of arsenic. Ten months after the transplantation the patient was still well and entirely without symptoms. Leschke suggests that the carrying out of such a procedure may give patients with tuberculosis of the suprarenal gland a sufficient period of restored health to permit a cure of tuberculosis and restoration of function in the remainder of the damaged gland and, may, therefore, offer considerable prospect of bringing about a permanent cure of the disease in a certain proportion of patients.

A New Procedure in the Treatment of Graves' Disease.—The well-established fact that residence in high altitudes is markedly beneficial to a large proportion of patients with exophthalmic goiter led HEINRICH LAX (*Klin. Wchnschr.*, 1928, **7**, 2295) to carry out a series of very carefully controlled observations on the treatment of a group of such patients in a cabinet in which they could be subjected to reduced atmospheric pressure. Repeated accurate determinations of the basal metabolism were made upon all patients and a group was retained untreated to serve as controls. In addition to this method of control the treated patients were studied for a period of four days in the air chamber with the pressure remaining normal—a fact unknown to them. The patients selected for treatment comprised those with clinically

typical cases of medium to severe degrees. The basal-metabolism readings before treatment varied from +30 to +100 per cent. Each patient was exposed daily to the reduced pressure treatment for a period of four hours and the treatment was continued for from two to three weeks. Forty patients were so treated; all other forms of therapy having been omitted for a period of four weeks prior to the institution of treatment. Of these 29 showed pronounced reduction in the basal metabolism, several became normal, and marked improvement was shown in the subsequent symptoms of the disease. These patients were observed for second periods of time up to nine months during which they maintained the improvement in most cases. Several patients who failed to improve were later sent to high altitudes where they also showed no response. The author believes that the rapid and temporary reduction in atmospheric pressure as produced in these cases is perhaps more beneficial than prolonged residence at a high altitude and he is under the impression that still better results are obtained when the atmospheric pressure in the chamber is suddenly changed several times during each period of exposure. He feels that these results indicate that the chief virtue of treatment in high altitudes is due to the reduction of atmospheric pressure. While holding this view he admits that other benefits result from residence in high altitudes but he feels that a preliminary period of treatment and observation in the reduced-pressure cabinet is of great value both as a therapeutic measure and as a method of determining in advance whether or not a patient should be sent to a high altitude.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Asthma in Children.—PESHKIN and FINEMAN (*Am. J. Dis. Child.*, 1929, **37**, 39) have compared the application of local passive transfer of human hypersensitiveness or the indirect method with the scratch and intradermal skin tests or the direct method. They tested 18 asthmatic children from seven months of age to fourteen years by each method, using 33 protein extracts. They used dried powdered extracts for the scratch tests and fluid extracts for the intradermal test. These children were watched over a period of two years. The total number of tests performed in this series was 3252. The total number of positive reactions ranging from questionable to 4+ obtained by the scratch technique with the direct method was 92. On checking up this group only 18 reactions were found in the same cases with the indirect method. The total number of positive reactions ranging from positive to 3+ obtained by the intradermal technique with the direct method was 104. Checking these cases with the indirect method, only 24 positive

reactions were obtained. Comparative tests between the scratch and intradermal technique with both the direct and indirect methods showed that the total number of positive reactions obtained by the scratch technique with the direct method was 92. Of these 80.5 per cent were negative with the indirect method. The corresponding tests with the indirect technique by the direct method showed 50 positive reactions. Of these 83.5 per cent were negative with the indirect method. The total number of negative reactions obtained by the scratch technique with the direct method was 496. Of these 3 per cent were positive with the indirect method. The corresponding tests with the intradermal technique by the direct method failed to give positive reactions with the indirect method. Three children with asthma and hay fever reacted negatively to pollen with both the direct and indirect methods of testing. They gave positive reactions by the conjunctival tests with the dry powder. This result emphasizes the value of the latter-mentioned technique which Peshkin previously claimed to be a rapid safe and reliable method in patients refractory to skin tests. The indirect method of testing employed as a routine measure, according to these authors, is unsafe and they feel that its employment as a substitute for the direct method even in especially selected cases is not practical.

Skin Reactions of Patients with Rheumatic Fever to Toxin Filtrates of Streptococcus.—Swift, Wilson and Todd (*Am. J. Dis. Child.*, 1929, **37**, 98) state that patients with rheumatic fever gave a higher proportion of positive skin reactions with filtrates of both indifferent and green streptococcus than did the non-rheumatic controls. Cases with active rheumatic fever gave a higher proportion of positive reactions with these filtrates than did those with inactive or cured rheumatic fever. Comparing the reactions with unheated filtrate with those with filtrates boiled for one hour, it was found that the boiled filtrate gave stronger reactions in most patients with rheumatic fever and weaker reactions in most patients with inactive or cured rheumatic fever. They did not find a close correspondence in the capacity of patients to give skin reactions with Dick toxin and filtrates of non-hemolytic streptococci. Positive reactions in patients with rheumatic fever seemed to depend more on the state of hypersensitiveness to certain products of streptococci than the specificity of any one type of streptococcus.

Congenital Stenosis of the Esophagus.—Beatty (*Brit. J. Child. Dis.*, 1928, **25**, 237) reviewed the literature comprising 50 cases of the congenital stenosis of the esophagus and adds 5 cases in his own experience. This anomaly is rare and there are two types. One is a membranous type, in which there is partial occlusion of the lumen by a fold of normal mucous membrane. The other is a nonmembranous type in which there is a localized reduction in the size of the esophagus. The stenosis may be situated anywhere in the esophagus, but the most common sites are in the lower and upper ends. The congenital type is characterized by an absence of pathologic changes in the walls of the esophagus in contradistinction to the acquired form of stenosis. There may be however, hypertrophy and dilatation above the obstruction. Other congenital abnormalities do not usually accompany this condition.

The onset of symptoms is usually in infancy, more commonly at the time of weaning. The most characteristic is the regurgitation of food unchanged in form within a few minutes after swallowing, and this is not associated with pain or nausea. Adult patients may be well developed and well nourished but some degree of infantilism so common in children and adolescence. In diagnosing this condition, Roentgen ray and endoscopic examination are most helpful. The prognosis in the membranous type is good when treatment is proper and complete recovery usually follows. In the non-membranous variety, the outlook is not unfavorable as regards life and some of the patients live to an old age, but in the latter form, the relief of symptoms is more difficult and severe restrictions in solid food are generally necessary throughout life. In treating the membranous variety, gradual dilatation with bougies is checked by endoscopic examinations until the membrane has been destroyed. In the non-membranous form, dilatation is likely to be successful, but is attended with considerable risk of rupture. In stenosis at the lower end, excision may be considered.

Classification of Heart Disease in Children.—Wilson, Lingg and Croxford (*Am. Heart J.* 1928, **4**, 197) observed 500 children ranging in age from two to twenty-two years and he found that four-fifths presented a history of rheumatic disease. Congenital heart defects occurred in 50. In 18 of these there was subsequent rheumatic infection. Children with possible heart disease, where systolic murmurs were heard between the second and fourth interspaces, retained the same physical signs without progress over a period of years. They found that the average age at the onset of the rheumatic infection was 7.3 years. In half the children the onset occurred between the ages of six and nine years. Rheumatic infection is principally seen in children of the grade-school age. It has been observed that from the age of twelve years the tendency to infection diminishes. Three-fourths of 413 children with a rheumatic history developed definite heart disease and the remaining one-fourth were potential heart-disease patients. The heart is probably always involved to some extent at the time of the first infection, although marked involvement was noted in only 63 per cent within one year of the onset. The associated manifestations of rheumatic infection were not indicative of the degree of heart involvement. Growing and joint pains seemed to bear the same relationship to heart involvement as polyarthritis or chorea. The degree of heart involvement was closely related to the number of attacks of carditis. In this series 12 per cent of the children died and 88 per cent of these deaths were due to rheumatic heart disease.

The Value of Parathyroid Hormone for the Organism.—Waltner (*Monatschr. f. Kinderh.*, 1928, **40**, 317) gives as one of the causes for rachitic disturbances in calcification the hypertrophy or increased function of the parathyroid glands. Increased function of the parathyroid glands in rickets mobilizes calcium from the bones or hinders the normal deposit of lime. With a marked decrease in the function of the parathyroid and a positive calcium balance, disturbances of the osseous system will occur. Experiments show that excess as well as deficiency of parathyroid hormone causes a change in the bones. The presence of a

certain amount of parathyroid hormone is necessary for a normal development of the skeleton. Removal of the parathyroid glands means absence of parathyroid hormone, and the blood cannot keep enough calcium absorbed in the intestines but deposits it into the soft tissue. Animals without parathyroid glands develop osteoporosis. When parathyroid hormone is present in excess, an increased consumption of calcium is the result. Calcium is particularly taken away from the osseous system. It can be seen from this that an excess of parathyroid hormone has the same effect as the lack of hormone. The phenomenon is analogous to the effect of insulin on the production of glycogen.

Paroxysmal Sneezing as an Equivalent of Paroxysmal Cough of Pertussis.—REICHLE (*J. Am. Med. Assn.*, 1929, **92**, 443) reports two cases and refers to a number of authorities. He feels that sneezing, if paroxysmal in character, may be of great value in diagnosing as an early symptom of pertussis. In certain young children the sneezing may supplant the cough either entirely or partly. These attacks of sneezing are typically convulsive, cause congestion of the head, cyanosis and exhaustion, and may end in expectoration of the usual tenacious mucus through the mouth and nose, as in the cough attacks. These spasms may be accompanied by coryza, inspiratory crow and vomiting. The cases reported in this article as well as those described in the literature have been moderately severe but not fatal.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Pathogenesis of Trichophytids. SULZBERGER (*Arch. Dermatol. and Syph.*, 1928, **18**, 891). This article contains a succinct and clearcut explanation of the present conceptions of the mechanism of development of trichophytids or secondary general eruptions associated with an allergic state of the individual following the development of a deep lesion due to fungus infection. The report covers the experimental production of hematogenous infection and the development of spontaneous lesions in guinea-pigs. Following intracardiac injection, the fungus was recovered from the blood stream at two distinct periods; that immediately following the injection, and again ten to thirteen days later. The second appearance of the organism in the blood stream is interpreted as spontaneous and as corresponding to the development of the allergy which is instrumental in the production of trichophytids. In 3 of 34 guinea pigs examined, the organism was recovered from the viscera (spleen and kidney).

Superficial Yeast Infections of the Glabrous Skin.—WHITE (*Arch. Dermatol. and Syph.*, 1928, **18**, 429) reports further on Cryptococcus (yeast) infections of the skin. Reference is had to the observations of Castellani (1927), Greenbaum and Klauder (1922), Beeson and Church (1926). The involution of artificially induced fungus lesions can be materially delayed, and their extension promoted by mechanical irritation, such as occurs with scratching. While cryptococci inhabit normal skins, a limited series of successful inoculations of cultures on their respective hosts indicates their possible pathogenicity in the syndrome known as seborrheic dermatitis, especially of the exudative type. The postulates of Koch have been fulfilled; the organism was recovered from the artificial lesion. It is suggested that some examples of infantile eczema may belong in this group.

Cryptococcus Epidermica.—WHITE and SWARTZ (*Arch. Dermatol. and Syph.*, 1928, **18**, 692) ascribe cutaneous infection with the cryptococcus to poor hygiene, particularly the wearing of unboilable clothing next to the skin. They differentiate the disease which they believe to be an entity, from eczema as such; soap eczema of Radcliffe Crocker; psoriasiforme eczema of Brocq; aberrant pityriasis rosea, which its patchy character and dry lesions may resemble; erythrodermie pityriasique en plaques disseminees; premycotic mycosis fungoides; tinea versicolor; and epidermophytosis. They treat it with an ointment containing mercurochrome 0.68 gm.; salicylic acid 2 gm.; petrolatum and hydrous wool fat, each 16 gm.—with varying degrees of success.

Hot Baths in Late Syphilis.—HOLLINGSWORTH (*Arch. Dermatol. and Syph.*, 1928, **18**, 736) directs attention to the ancient lineage of this procedure and records its inapplicability to 5 cases which were treated by this method with weakening effects, and no significant therapeutic response. The reported experiments on rabbits do not encourage the belief that the method will be applicable to human syphilis. Massa, in 1563, summarized the situation and dismissed the procedure in words applicable today.

Serologic Discord in Latent and Treated Syphilis.—SHEPLAR, LYONS and MACNEAL (*Arch. Dermatol. and Syph.*, 1928, **18**, 742) compared a Wassermann procedure using the Kolmer and a cholesterinized beef-heart antigen, with the Kline, Kahn and the Vernes procedures. They found that by making up their series from nonsyphilitics and patients with untreated early syphilis it was possible to secure from 90 to 95 per cent agreement in the results of the three procedures. On the other hand, if the series were made up from treated and latent syphilitic patients, irreconcilable differences between the results of the tests developed. To this they apply the apt term "serologic discord." They suggest that the variations observed in the testing of a single serum are due to the fact that there is not one but a number of antigenic elements in variable proportion in the serum of the latent and treated syphilitic patient and that each test procedure singles out or reacts to certain of these, producing a variability in results that must be met by the use of several test methods in examining of each serum.

Antenatal Treatment of Syphilis.—NABARRO (*British J. Ven. Dis.*, 1928, **4**, 107) reviews the literature of the subject and the article is correspondingly difficult to abstract. Significant points may, however, be quoted. Antenatal treatment of the syphilitic mother dates to the 17th century. Johnson, in 1877, wrote on the subject in the United States. The results of Boas and Gammeltoft, published in 1925, are the most complete in Europe. The period of observation of the healthy children ranged from six months to fifteen years. The following table is a valuable summary:

Treatment of mother.	No. of cases.	Children (per cent).	
		Syphilitic.	Healthy.
Syphilis not treated	201	96.5	3.5
Mercury before pregnancy; no treatment during	87	90.0	10.0
Arsphenamin before pregnancy; no treatment during	15	80.0	20.0
Mercury during pregnancy	111	72.0	28.0
Arsphenamin before pregnancy, mercury during	26	27.0	73.0
Arsphenamin during pregnancy	98	19.5	80.5
Arsphenamin before and during pregnancy	7	14.5	85.5

Ballantyne from the Royal Maternity, Edinburgh, reports 5.1 per cent stillbirths in 138 supervised and treated syphilitic mothers as compared with 60.6 per cent stillbirths in 33 untreated mothers. Nabarro examines the child every three months the first year, twice the second and third years and once annually thereafter. It has been shown that a woman may give birth to a syphilitic child twenty, twenty-four, twenty-six and even thirty-seven years after infection. In the Boas and Gammeltoft series, 55 of 483 pregnancies in untreated syphilitic women produced 48 syphilitic and 7 healthy children from four to twenty years after infection. Observers agree that the mother should be treated during each pregnancy and early in the course of the pregnancy if the child is to receive the greatest possible protection.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Results of Olshausen Suspension Operation.—One of the simplest operations for the suspension of a retroverted uterus is that which has been described by Olshausen and which consists of suturing the round ligaments to the abdominal wall. In order to determine the end results of this operation, BARROWS (*Am. J. Obst. and Gynec.*, 1928,

16, 61) has made a comparative study of this operation and the Baldy-Webster and Simpson-Montgomery types of operation. Of 135 Baldy-Webster operations, 109 were traced with 88 per cent excellent results; of 211 Simpson-Montgomery operations, 164 were traced with 93 per cent excellent results; of 571 Olshausen operations, 432 were traced with 92 per cent excellent results. In this series of 571 Olshausen operations there were 7 infected wounds, the silk ligature had to be removed in 1 case, a round ligament pulled away from the abdominal wall in 3 cases, there was one sinus in the abdominal incision and in 2 cases there was a potential hernia near the site of the knot. The author states that by using the braided-silk ligature doubled, one is able by tension in tying the knot to cause sufficient application of the round ligament to the solid structures of the abdominal wall without serious trauma to the ligament or danger of cutting through its muscular tissue. In spite of the fact that previous descriptions of the operation have stressed the tight tying of the silk knot, he believes that it is important not to tie the ligature tight enough to cut through the ligament early or late and that many failures have been avoided on this account. Briefly, therefore, his analysis of the situation showed that the operation compares favorably with the other types of round ligament suspension, including its reaction to pregnancy. In spite of theoretical objections to the technique of the operation, it is seldom followed by intestinal obstruction, the silk ligatures rarely give trouble, while the ease and rapidity of accomplishment as well as the absence of unnecessary trauma to adjacent structures recommend the operation.

Extraction of Hair Pin from Bladder.—The various types of foreign bodies which have found their way into the female urinary bladder would make an interesting museum exhibit at a hardware show and one of the commonest articles is, as may be supposed, that universal tool of the female of our species, the hair pin. Without going into the details of why it gets into the bladder so frequently, it might be of value at some future time to be aware of the method which SIGWART (*Zentralbl. f. Gynäk.*, 1928, **52**, 1550) employed for the removal of a hair pin, especially when an operating cystoscope and forceps are not available. Having located the pin through the cystoscope, he took an ordinary ureteral catheter and cut off the tip of it. The wire stylet which is supplied with the catheter was then passed through its lumen and a loop made on the distal end of the wire after it had passed through the catheter. This loop was made small enough to pass through the catheter channel of the cystoscope, yet large enough to slip over the end of the hair pin. After introducing this catheter into the bladder through the cystoscope, the loop was slipped over one of the ends of the hair pin and then gently worked upward until it was at the center of the elbow of the pin. The cystoscope was then withdrawn over the catheter and then the catheter was gently pulled through the urethra, drawing the hair pin after it without causing the patient any pain.

Cause of Uterine Myoma Sterility.—From the Gynecological Institute of the Kyoto Imperial University comes an interesting experimental study by UCHIGAKI (*Jap. J. Obst. and Gynec.*, 1928, **11**, 61) who investigated the cause of sterility in cases where there is a very small myoma,

almost impalpable, after the removal of which the patient easily conceives. These growths are so small that it is hard to explain the sterility on a mechanical basis. Working with rabbits, he found that the continual injection of an extract prepared from a myoma causes atresia and degeneration of the ovarian follicles, weakness of the muscular layer of the uterus and degeneration in its mucous membrane. These injections markedly accelerated the movements of the excised uterus and atropin and scopolamin have no controlling power over this acceleration so that the point of attack of these extracts is presumably in the muscles themselves. When rabbit were impregnated and then given these injections they usually failed to conceive. In another experiment, simple laparotomy was performed with instant closing of the abdomen and copulation was effected after a certain period of time. In 6 cases, there were 4 instances of conception. However, in 6 other rabbits a piece of cartilage was transplanted into the wall of the uterus to simulate the foreign body action of a myoma and none of them conceived. After the cartilage was removed, 2 of them conceived. The experiments were all well controlled and Uchigaki concludes that the toxic influence of the myoma element on the ovarian follicles, its acceleration of the muscular activity of the uterus and the circumscribed presence of myoma nodules acting as foreign bodies are all factors in the production of the sterility associated with uterine myomata.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Concerning the Etiology of Postoperative Abscess of the Lung. A Review.—As a pathologic entity, pulmonary suppuration embraces a variety of acute and chronic lesions, capable of differing greatly in their mode of production, their morphologic characteristics, and their response to treatment. One of the outstanding manifestations of pulmonary suppuration is abscess which also may occur in various forms, each of which may be due to quite different causes. Among the commoner types of lung abscess is that which is now recognized as developing after surgical procedures. It has been estimated that approximately one-third of nontuberculous abscesses of lung follow operations (Wessler, 26 per cent; Lockwood, 43 per cent; Heuer and MacCready, 26 per cent; Homans, 57 per cent; Singer and Graham, 32 per cent; Lambert and Miller, 25 per cent; Whittemore, 66 per cent; Hedblom, 21 per cent; Lord, 42 per cent; Cutler and Schlueter, 29.6 per cent [515 of 1908 cases collected from literature, including those given above]). Of the postoperative pulmonary abscesses, a relatively high proportion have followed tonsillectomy. For example, in further analyzing the statistics of the authors just mentioned, one finds that the

percentage varies from 25 to 80 (Wessler,[1] 80; Lockwood,[2] 70; Heuer and MacCready,[3] 25; Homans,[4] 54; Singer and Graham,[5] 73; Lambert and Miller,[6] 52; Whittemore,[7] 72; Hedblom,[8] 32; Lord,[9] 51; and Schlueter and Weidlein,[10] 52—the same collected series previously reported by Cutler and Schlueter[11]). This apparently high frequency (*circa* 50 per cent) has resulted in the idea that pulmonary abscess, as a postoperative complication, is virtually peculiar to tonsillectomy. As a matter of fact, however, closer investigation does not substantiate this conception. The relevant statistical data, compiled from provincial sources, reveal a wide variance in the incidence of posttonsillectomic abscess of lung—varying from none in 20,000 and 3500 cases by Lyman,[12] and Crowe and Scarff,[13] respectively, to two in 20,000 by Hedblom[8] and two in 12,045 by Herb,[14] to the astonishingly high calculation of one in every 358 tonsillectomies (Glowacki[15]). On the other hand, Moore,[16] after a comprehensive national survey comprising about 450,000 cases, found that pulmonary abscess occurred once in every 2500 operations for the removal of tonsils. Moreover, it must be kept in mind that tonsillectomy is a very common operation, as a recent governmental report[17] has shown, and that "about one-third of all operations since 1924 among the American urban population were for the removal of tonsils and adenoids."[18]

Nevertheless, while it may be true that lung abscess is a relatively infrequent posttonsillectomic complication and that it follows this operation no oftener than surgical procedures in any other septic field, its actual incidence is so alarmingly high as to become a serious problem. The realization of this has stimulated an unprecedented activity in clinical and investigative fields, not only of otolaryngology but also of many other departments of medicine and surgery, with a view to obtain a clearer understanding of the factors involved so that appropriate prophylactic and remedial measures might be ascertained.

While these studies have embraced practically all of the salient phases of the subject, most of them have been motivated by the desire to determine the ways in which the infection can be transported from the operative site to the lung. Without delving into detail, it can be said that the results of these researches have evolved two outstanding theories regarding the *modus operandi* of postoperative pulmonic abscess, namely, the "aspiration" and the "embolic." Naturally, the former has to do with the respiratory and the latter with the cardiovascular system. Although Smith[19] says that "at present each (theory) has about an equal number of adherents," Schlueter and Weidlein[20] state that "in a census of recent writers, forty declare themselves in favor of aspiration, while only ten favor embolism as the direct cause of lung abscess."

As the rivalry between these two schools of thought is keen; as the controversy is acute; as the champions of each emphatically maintain that the solution to the problem is of cardinal importance in pointing the way to the prevention of this dread posttonsillectomic sequela; and as Smith[19] puts it, "the evident conflict between these theories is an obstacle to the adoption of satisfactory methods of prevention," the purpose of this communication is to present, briefly, the findings of the more recent available investigations pertinent to the question.

"Embolic" Investigations.—In 1923, Fetterolf and Fox[21] studied the reaction of the paratonsillar tissues in recently tonsillectomized dogs. Inasmuch as they found areas of hemorrhage and necrosis, bacteria, and sterile or septic thrombi in the traumatized bloodvessels, they concluded that "while realizing that posttonsillectomy lung complications may at times be of inspiratory origin we believe that such origin is not as common as has been thought," and considered it quite possible for small emboli from the operative wound to cause septic infarcts in the lung.

Recognizing the important part played by emboli in the causation of other types of postoperative lung complications, as suggested by Mikulicz,[22] and believing that pulmonary abscess might have a similar etiology, Cutler and Schlueter[11] and their co-workers, Holman,[23] Weidlein,[24] and Holloway[25] have conducted numerous experiments on dogs "in the hope that further proof might be found for the concept that a large proportion of such complications are due to embolism from the operative wound."[26] By liberating into the venous circulation artificially enclosed septic emboli, they were able to produce abscesses of the lung with great regularity. In view of the fact that their attempts to cause lung abscess by the intrabronchial injection of infected materials failed, they believed that their results furnished further evidence in favor of the embolic theory of pulmonary abscess.

Because such abscesses in the experimental animal differed from those commonly found in human beings in their failure to become chronic, and considering the factor of chronicity to be of major importance, Herrmann and Cutler[27] succeeded in inducing chronic abscesses in the canine lung by the introduction, according to the standardized technique, of emboli infected with material from the lesions of human pyorrhea alveolaris. The authors regarded their findings as indicating that chronicity of the experimental canine pulmonary abscess is dependent upon the presence of a certain group of anaërobic bacteria frequently encountered at the gingival margins in pyorrhea.

Further experimental observations concerning such factors that might determine chronicity as cough, foreign bodies and types of microörganisms have been reported by Weidlein and Herrmann.[28] After investigating both the respiratory and circulatory routes of infection, they concluded that while the action of cough, as described by Brown and Archibald,[29] exerts a determining influence on the chronicity of pulmonic suppurative processes, it alone is not able to account for the duration of the lesions as found in man; that the rôle played by a foreign body as a source of irritation is probably a minor one unless actual injury to the bronchial wall results; that the presence of certain anaërobic bacteria (spirochetes, vibrios and fusiform bacilli) is of importance in the production of lung abscess; and that it is doubtful whether pulmonary abscesses can be produced by the introduction of material into the respiratory tree under conditions of only partial occlusion. These workers also state that "whether these infectious agents reach the lung in man by way of air passages or the blood stream is still a debatable point. However, under experimental conditions, insufflated material must actually block the air passages completely, as well as injure the bronchi, before an abscess can be produced."

Regarding the bacteriologic phases of the subject, it has been demon-

strated that the duration of a pulmonic abscess may be influenced not only by the immunological attributes of the host, but also by the nature of the causative microörganisms. For instance, van Allen[30] has shown that abscesses, experimentally produced by Staphylococcus aureus, heal within four weeks; that, according to Holman, Chandler and Cooley,[31] a mixture of the usual pyogenic bacteria prolongs the healing time; and that abscesses resulting from fusospirillary forms persist as long as two or three months (Weidlein and Herrmann[28]). These fusospirillary organisms are virtually ubiquitous in the oral cavity, being found in great numbers at the gingival margins and in the actinomyces—like granules of tonsillar crypts, as well as in pulmonary abscess and gangrene (Davis,[32] Pilot and Davis,[33] Pilot and Bram,[34] Pilot, Davis and Shapiro,[35] and Pilot and Davis[36]).

In order to ascertain whether a lung abscess infected with an organism commonly associated with only acute lesions may be rendered slow to heal by the superimposition of bacteria which are capable of causing chronic pulmonary processes, Adams, van Allen and Day[37] produced lung abscesses in dogs by the embolic method described by Cutler *et al.*,[11,73] and then introduced, intratracheally, sputum freshly obtained from individuals with chronic pulmonary suppuration. It was found that staphylococcic abscesses, which regularly heal before thirty days, frequently persisted for a longer period. The authors raise the question whether in man postoperative lung abscess which occurs from infected embolus may become superinoculated by mouth organisms through accidental insufflation, and thereby assume the characteristics of bronchogenic abscesses.

(*To be concluded in May issue.*)

RADIOLOGY

UNDER THE CHARGE OF

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Fusospirochetal Pulmonary Gangrene.—Two cases are reported by Doub (*Radiology*, 1928, **11**, 333). One occurred after operation for inguinal hernia and the patient died. In the second case the disease came on independently and the patient recovered after evacuation of a pulmonary abscess and cauterization of the abscess cavity. An abscess was revealed by the Roentgen ray in both instances. Fusospirochetal gangrene has become a recognized clinical entity in recent years. Bacterial studies of the sputum reveal fusiform bacilli, spirochetes and other bacteria, especially streptococci. Experiments indi-

cate that these organisms are saprophytic and that devitalized tissue is necessary for their growth. Clinically the disease simulates a bronchitis or bronchopneumonia except that the sputum is always fetid. Roentgenologically the lesion resembles an abscess or gangrene, but it progresses more rapidly than an ordinary infection. Administration of arsphenamin is the accepted treatment in the earlier stages, and operation in the later chronic stages.

Radiotherapy in Actinomycosis. Approximately 30 cases of intra-abdominal or intrathoracic actinomycosis have been observed at the Mayo Clinic from 1920 to 1925, and these are reported in tabular form by DESJARDINS (*Radiology*, 1928, **11**, 321). In 26 cases the disease affected chiefly the intestinal or pelvic structures. Thoracic structures were the principal seat in 11 cases and in 7 the lesions were in both the thorax and abdomen. Treatment in most cases consisted of a combination of drainage, the administration of iodides internally and Roentgen irradiation of the abdomen or thorax. Radium was also given at some time in 8 cases. When actinomycosis attacks the intestine or lungs the disease often becomes extensive before its character is recognized. It is not surprising, therefore, that the series shows a very high mortality. Nevertheless, the therapeutic combination commonly resulted in amelioration, and several patients were apparently well after one or two years.

Clinical Difficulties Encountered in Cutaneous Roentgen Therapy.—Objectionable conditions that are characteristic of many skin diseases are often attributed to treatment with Roentgen rays or radium, says MACKEE (*Am. J. Roent. and Rad. Therap.*, 1928, **20**, 121). Spontaneous exacerbations of certain diseases are common, topical remedies may cause alarming symptoms, additional affections may develop and a number of dermatoses have objectionable, disfiguring and even dangerous sequelæ which may erroneously be attributed to irradiation. The author, therefore, thinks that irradiation treatment should be conducted or supervised by a dermatologist. Its intelligent use requires a thorough training in cutaneous medicine. It is important to know what dermatoses are amenable to irradiation and what the therapeutic response should be. Such knowledge will do much to prevent useless or harmful treatment. If a disease fails to yield to the Roentgen ray or radium in a normal manner they should be discontinued and all the resources of cutaneous medicine employed to combat the affection. In fact, it is preferable to depend on these resources as much as possible in every case and from the beginning of treatment.

Osteochondritis Dissecans.—Observation of several cases of osteochondritis dissecans in unusual situations is the basis of a paper by GEYMAN (*Radiology*, 1928, **11**, 315) on this subject. The most commonly reported sites are the lateral portion of the mesial condyle of the femur and the external condyle of the humerus. In the author's first case a fragment of bone had become detached from the mesial articular facet of the patella near the distal border, leaving a small oval defect in the patella which was visible in the roentgenogram but overlooked prior to operation. In the second case the fragment had come from

the lateral portion of the external condyle of the knee. The third case was one in which the left hip joint was affected; roentgenograms revealed a rather large area of subchondral rarefaction in the head of the femur, and within the cavity lay an apparently completely separated bony fragment. In the fourth case the defect and fragment *in situ* were in the external condyle of the humerus. A history of trauma was obtained in 3 of the 4 cases.

Roentgen Studies of the Bones in Certain Diseases of the Blood.—In several cases observed by KARSHNER (*Am. J. Roentgenol. and Rad. Therap.*, 1928, **20**, 433) at the Children's Hospital, roentgenograms of the bones have aided the diagnosis of certain diseases of the blood. In von Jaksch's anemia—anemia infantum pseudoleukemica—there is a decided thickening of the medullary portion of the cranial bones, with thinning of the outer and inner tables. Early the bone marrow is mottled and spongy; later striations of new bone perpendicular to the tables appear. The pelvis, spine, ribs, scapulæ and bones of the hands and feet are very porous; the metacarpals are expanded; the cortex of the long bones is very thin and the medulla is unusually transparent. In a case of leukemia just before death, there was a slight rarefaction of the larger bones. The periosteum of both humeri and femora was raised, and in places new bone was laid down perpendicular to the shaft. The only positive Roentgen ray finding in a case of chloroma was widening of the cranial sutures, the long bones being negative. The Roentgen ray changes of hemophilia are the result of hemorrhage into the joints and adjacent bone. Any joint may be involved, most commonly the knees, elbows, ankles, hips and shoulders. In the early stage there may be effusion of blood into the joints with or without calcification. The joint capsule may be thickened and there may be lipping similar to that of hypertrophic arthritis.

NEUROLOGY AND PSYCHIATRY

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Lipodystrophies: Report of Seven Cases.—LLOYD H. ZIEGLER (*Brain*, 1928, **51**, 147) presents the clinical histories of 7 patients with lipodystrophic disturbances. He considers nervous symptoms of varying degree and nature to be common to the group. Five of the 7 cases either had, or showed some signs tending toward, diabetes mellitus. He states that the chief hypothetical causes are neurotrophic and endocrine disturbances, alteration of fat metabolism, race and heredity,

infection and congenital defect. As to treatment, he reports that paraffin injections to remedy the facial appearance have not been permanently successful. A few patients have been benefited by rest in bed, ovarian extract and whole pituitary.

The Clinical Differentiation of Psychogenic and Physiogenic Disorders.—R. D. GILLESPIE (*Brain*, 1928, **51**, 254) records 9 cases in which the differentiation of a psychogenic from a physiogenic disorder presented a serious difficulty. In a study of 13 cases he found 9 erroneous diagnoses of which 5 were of organic disease where only psychogenic symptoms were present and in 4 a diagnosis of psychogenic disorder was made when the condition was one of organic disease. He advances the following criteria for differential diagnosis. (1) The nature of the physical signs present. If the physical signs are relevant to the complaints it is not necessary to go further for diagnosis except for the purpose of assessing any suspected psychogenic element in the disability produced. If the physical signs are not apparently relevant it is necessary to investigate further. "There is a presumption of psychological origin for all physical signs that may be produced either by the direct effect of emotional disturbance or by the patient's volition." (2) The type of history of the illness. He states that there are common types of history that are indisputably those of a physical disorder. "Where the onset of certain signs and symptoms coincides in time with certain events, it is justifiable to suspect strongly an association between the two. Where there is a repeated coincidence of symptom and provocative situation, the suspicion is strengthened." (3) "A general setting of psychic disequilibrium is necessary for the development of a psychogenic disorder in response to external factors." (4) The personality make-up of the patient is of great importance as aberration from the average types of personality weigh the balance in favor of the psychic origin of the illness. (5) The mental attitude of the patient to his signs and symptoms. The neurotic shows deviations from the normal attitude either in an excess or defect of concern, together with a lack of persistence and determination in carrying out therapeutic recommendations. (6) The purpose which the illness seems to fulfill. "Where there seems to be nothing but disadvantage accruing, and when there is little discoverable cause for dissatisfaction . . . the psychic origin of symptoms must be doubtful. But even where a definite advantage seems to be gained, this may be an accident."

Are the Feeble Minded Criminals?—WALLACE (*Ment. Hyg.*, 1929, **13**, 93) calls attention to the fact that when the class of feeble minded included only idiots and imbeciles the term crime was almost unknown in the field of mental deficiency. With the advent of intelligence tests and discovery of the moron group criminality in connection with the feeble minded became conspicuous. He states that if feeble mindedness in itself is a cause of criminality the two should appear in direct ratio and the greater percentage of criminals should be found in the lower grades of the feeble minded. The high percentage of feeble minded in the delinquent and criminal class (15 to 30 per cent) he believes would be modified by considering certain important factors that have a bearing upon the discovery and confinement of delinquents. First of all, there

is a large number of individuals who are not delinquent but whose mental level would place them in the feeble-minded group. Also the greater number of feeble minded who are delinquent are quickly discovered while a large percentage of persons of normal intelligence escape. Especially he believes this to be true in the case of illicit sex practices among girls. Again, the feeble minded have neither influential relatives to intercede for them nor the ability to adequately defend themselves. He would divide mental defectives who come in conflict with the law into two groups: "Delinquent defectives" in which the mental defect is the major abnormality; and "defective delinquents" in which the delinquency is the primary consideration and in which the defect is primarily in the field of social adjustment. "If two cross sections of the population could be studied from a psychiatric point of view with the object of ascertaining what material it is that makes for positive, active criminality, it is doubtful if the greater preponderance of that material would be found in the section of the population whose mental levels are below a 75 *I. Q.* than in the section whose mental levels are above 75. The feeble minded, quite in common with the rest of the population, have two kinds of intelligence—mental intelligence and social intelligence, the only difference being that the mental intelligence in the feeble minded is not on so high a level. It is the balance or imbalance, however, of these two intelligences in the individual that makes for social adjustment or social failure in all mental levels."

The Sex of Mentally Deficient Individuals.—BRIDGMAN (*Ment. Hyg.*, 1929, **13**, 62) classifies according to the Binet scale 3675 individuals with *I. Q's* of less than 90 and analyzes them according to sex. She finds a preponderance of males in the idiot, borderline and dull normal groups while there is a preponderance of females in the imbecile and moron groups. She considers that these differences may be based to some extent upon variations in the type of delinquency and the type of supervision between the sexes. She states that these considerations do not, however, cover the discrepancies and feels that we must seek elsewhere for other factors. The construction of the test itself is possibly a factor in bringing out differences between the sexes. She analyzes the data on the basis of nationality and finds some variations here, the consideration of which leads her to the conclusion that the social element involved in the selection of cases to be brought to the clinic is probably the basis of discrepancies shown.

Mental Hygiene in the Public Schools.—WILE (*Ment. Hyg.*, 1929, **13**, 70) would apply the principles of mental hygiene to every child in school. As education is a state problem and the normal school forms the point of departure for the training of teachers he would begin his program with an extension of the training-school courses to include training in mental hygiene together with courses familiarizing teachers with the educational and emotional reaction systems of children. There should also be courses in the interpretation of spychometric tests and education along the lines of the accepted modes of providing and developing remedial teaching. To produce any effective results he believes that mental hygiene clinics are necessary and should be provided by the state if not already available through some other source. He would

recognize the school system on the basis of an ungraded class to which all children entering the school would be admitted for the purpose of study and classification. Every child in this clearing class would have a careful physical examination upon entering. Psychologic tests and other special studies would be made while the child is in this class, prior to his assignment to any special group.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Fate of Colloidal Iron Administered Intravenously.—In this article POLSON (*J. Path. and Bact.*, 1928, **31**, 445) presents a study of the distribution and fate of large doses of dialysed iron following intravenous administration to rabbits. The experiments were also used as an attempt to produce in rabbits a lesion similar to hemochromatosis in man. The animals were given large doses of iron and at varying intervals after the last dose they were killed and their organs examined histologically and chemically. The immediate effects depended upon the size of the dose and upon the rapidity with which it was administered. If any single dose was too large or given too quickly, the animal had convulsions, died, and on postmortem examination showed pulmonary embolism as the predominant picture. Where more prolonged study was followed, however, it became apparent that there were two principal results of the administration. These were: (1) Embolism, and (2) ingestion of iron by phagocytes derived from the liver, spleen and bone marrow. The greatest amount of iron in the lungs was as emboli in the vessels. No pulmonary infarction was noted and no iron was demonstrable in the bronchial epithelium. Phagocytosis was evident at the end of a week and was well advanced at the end of two weeks. The active cells were endothelials derived from the lung endothelium and large spheroidal cells, endothelial in type, of doubtful origin. The portal tracts were free from iron at all stages, but the Kupffer cells showed great avidity for the metal. These cells early became charged with iron. Subsequently, they became detached from the capillary walls and at the end of one week were seen in the lumina, later fusing into large multinuclear cells. While iron was evident in the Kupffer cells practically from the beginning of the experiments, it was only at the end of two weeks or more that it was found in the periphery of the liver lobules. A comparison of the lung and liver iron content was interesting, showing that in the shorter (three-day) experiments the ratio of lung iron to liver iron was 2.4 to 1. (After a single dose, the lung iron varied directly with the degree of embolism.) In

the longer experiments this ratio was reversed, the ratio at one week being 1 to 1, and at two weeks 1 to 2.1. It was thus apparent that by some unknown process the greater part of the lung iron ultimately reached the liver. The phagocytes of the spleen showed early avidity for the iron. These massed together and during the second week disintegrated, leaving iron depots in the splenic pulp. The Malpighian bodies were indifferent to the iron. Iron accumulated in the thoracic and abdominal lymph glands. Embolism of renal glomeruli was sometimes noted as an immediate effect. Iron did not appear in the tubules before two weeks, unless the tubules had been previously damaged. The iron content of the bone marrow rose toward the end of the second week. Iron was also noted in the cecum, in the epithelial cells of the mucosa and in the endothelial cells of the submucosa—facts which tend to verify the theory of at least partial excretion *via* the large bowel. In all other organs, iron was only found in the endothelial cells of the capillaries. Hemosiderosis was very readily produced. In even short experiments, the liver iron content was at least doubted.

Experimental Chronic Abscess of Lung.—Abscess of the lung has been produced experimentally by a number of investigators but it has been found more difficult to reproduce the chronic type comparable to the postoperative pulmonary abscess in man. HERMANN and CUTLER (*Proc. Soc. Exper. Biol. and Med.*, 1928, **26**, 28) found that arterial emboli, infected with spirochetes, fusiform bacilli and other mouth microörganisms from a patient with pyorrhea alveolaris, when implanted in the pulmonary tissue produced chronic abscesses identical in most respects to those in man, namely, thick walled, lined with a dark gray necrotic membrane, of a foul odor and containing exclusively anaërobic bacteria. The same types of organisms introduced by way of the bronchi did not give this result. ADAMS, VAN ALLEN and DAY (*Proc. Soc. Exper. Biol. and Med.*, 1928, **26**, 163) produced acute abscesses by emboli with Staphylococcus aureus which healed within four weeks but if ten days after the production of the embolic infection the lungs were insufflated with bronchiectatic sputum (which alone gave no abscesses), there resulted chronic abscesses. The latter authors, therefore, raise the question whether in man postoperative lung abscess which occurs from infected embolus may become superinoculated by mouth organisms through accidental insufflation and thereby assume the characteristics of bronchogenic abscesses.

Types of Tubercle Bacilli in Bone and Joint Tuberculosis.—The great importance of knowing more about the source of the tubercle bacilli in the extrapulmonary infections with tubercle bacilli makes this report by GRIFFITH (*J. Path. and Bact.*, 1928, **31**, 875) particularly valuable. The summary of 5 series of cases from Great Britain showed that from tuberculous children under ten years of age with extrapulmonary infection the bovine type of bacillus was recovered in about 30 per cent, while this percentage was reduced to 8 in those over ten years and no bovine infection was found in any patient aged twenty-five years or over. The difficulties in determining the type, the distribution in various bones and joints, the question of the portal of entry and many other problems of tuberculosis are here authoritatively discussed.

HYGIENE AND PUBLIC HEALTH

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The Health Record of University Students as Related to Tonsillectomy.—FORSYTH (*Pub. Health Reps.*, 1929, **43**, 560) made a study of approximately 1000 people, university students, with the idea of ascertaining whether the previous removal of tonsils materially affected the status of the individual with respect to health at the time of admission to the university and subsequently during his or her stay in the university. The group covered 703 individuals who had not had their tonsils removed, and 275 who had had their tonsils removed. There was little or no difference to be ascertained between the conditions in the two groups, although there was just a suggestion of some advantage in the group free of tonsils in general nutrition and general health grade. It was pointed out that the tonsillectomies must have been done on persons who were having some trouble and particularly subject to illness, and that the operations must have enabled that group to overcome the handicap and to enjoy health approximately equal to that of other students.

The Immunologic Relationship of Alastrim and Mild Smallpox.—LEAKE and FORCE (*Hyg. Lab. Bull. No.* 148, April, 1927) discuss briefly the literature on "alastrim" of Brazil and other parts of the world with special reference to its possible identity with smallpox. These officers detail their experiments, which were designed to show the immunologic relationship between "alastrim" as represented by strains from the West Indies and smallpox of the United States and vaccinia. The essential points of the summary are as follows: "A vesicopapular eruption was regularly produced in monkeys, through three generations, by inoculation with material, the sources of which were pustule contents, from three Jamaican patients with alastrim. Crusts from a Haitian patient with the same disease produced a similar eruption in two monkeys. Crusts from two American patients with mild smallpox (District of Columbia and West Virginia) produced similar eruptions in monkeys through three generations. Two monkeys successfully inoculated with alastrim were completely immune to vaccine virus thirteen and seventeen days later; the first of these was partially immune (gave a modified reaction or vaccinoid) to vaccine virus seventy-nine days after the alastrium inoculation. A monkey successfully vaccinated with vaccine virus was completely immune ten days later to alastrim and to smallpox inoculation. A monkey successfully inoculated with smallpox was com-

pletely immune twenty-two days later to alastrim and to smallpox. Another monkey successfully inoculated with smallpox was partially immune (gave a modified reaction or vaccinoid) to vaccine virus seventeen days later. Two monkeys successfully inoculated with alastrim were completely immune to another inoculation of alastrim thirteen and twenty-two days later, respectively, and the first of these was completely immune to a third inoculation of alastrim and an inoculation with smallpox eighty-four days after the first inoculation. Rabbits inoculated with alastrim showed some immunity to vaccine virus; those receiving two inoculations (directly with human material and with the first monkey generation) showed a higher degree of immunity than those inoculated once (with the second or third monkey generation. This immunity was not different from that shown by rabbits which had been inoculated with smallpox (second monkey generation)). None of these rabbits showed marked lesions from their smallpox or alastrim inoculations. The fact that definite cross immunity exists between alastrim and mild smallpox and between alastrim and vaccine virus is additional evidence of the identity of alastrim and mild smallpox."

Malta Fever: A Problem for State and Municipal Laboratories.—HARDY (*Pub. Health Reps.*, 1929, **43**, 503) points out that the previous work of Evans has shown a very close relationship between the organism of Malta fever and that of contagious abortion of cattle and surveys briefly the reports of Malta fever of bovine origin. In routine testing of the blood for typhoid fever it was made the rule to run also tests for Malta fever; during the time that the work was in progress 783 examinations were made which resulted in the disclosure of 41 cases of typhoid and 31 cases of Malta fever, which is held to indicate that in Iowa at least Malta fever presents a health problem comparable to that presented by typhoid. In the great majority of cases the physician had not suspected Malta fever and Hardy believes that in the past only the prolonged and severe cases have been studied while the milder cases and those of shorter duration have in general escaped detection. The technique of carrying out the reactions is given in detail.

Benzocain-Chaulmoogra Oil in Treatment of Leprosy.—JOHANSEN (*Pub. Health Reps.*, 1927, **42**, 3005) notes that chaulmoogra oil has been used for a long period in the treatment of leprosy and calculates, therefore, that it has some virtue in the treatment of the disease. It is pointed out that oral administration is accompanied by disagreeable features and that introduction by the intramuscular route, either of the crude oil or of its refined products, is painful and ordinarily not well tolerated by lepers. The obvious disadvantages of intravenous administration are noted. An attempt was made to overcome the disadvantages of the intramuscular injection by adding to the oil 3 per cent of benzocain, together with 10 per cent of olive oil. The dose of this preparation was from 5 to 8 cc. although in a few cases almost double the latter amount was given. It was found that the oil was absorbed within forty-eight hours in most cases and rarely could any indication be found after three days. Of 24 cases 6 showed marked improvement, 12 showed moderate improvement, 5 showed slight improvement, and 1 was not improved. No claim is made that this treatment will cure leprosy; it was felt, however, that it is worthy of a further trial.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF FEBRUARY 18, 1929

Observation on the Differentiation of Bloodvessel Endothelium as Seen on the Yolk Sac in Living Fundulus Embryos.—E. R. CLARK and L. CLARK (from the Department of Anatomy, University of Pennsylvania). The method of study was similar to that used by Stockard,[1] namely, the observation of the living developing transparent egg of fundulus. The results agreed in all essential points with those of Stockard. Thus we saw the migration from the region of the embryo of cells which gradually showed the three-fold differentiation into orange chromatophores, black chromatophores and bloodvessel endothelium; also the localized differentiation of the erythroblasts and erythrocytes in a mass continuous with a mass in the posterior portion of the embryo proper. Moreover, we found that, over most of the yolk, and until circulation was established, the bloodvessel endothelium differentiates in the entire absence of erythroblasts and erythrocytes.

We were able to add the following points to Stockard's observations. The preëndothelial cells, or "angioblasts," move out over the yolk as an anastomosing network of homogeneous, hyalin-appearing, mesenchyme-like cells. They may be seen as early as thirty hours. In the interstices cells of a slightly coarser type wander about, and (between the forty-fifth and fifty-fifth hour) develop either orange or black granules and become chromatophores, as described by Stockard. In addition are numerous small, round cells which move actively among the other cells, which divide frequently and rapidly, and which persist after the other types have differentiated, the ultimate fate of which has not yet been determined.

Through the period from forty to forty-six hours the angioblast cells continue to move actively over the yolk, increase by mitotic division and enlarge by the formation of longer processes which connect with neighboring angioblast cells. Rather suddenly, at about forty-six hours, there occurs a remarkable change in the angioblast cells, affecting enormous numbers over the extra-embryonic area simultaneously. The hyalin appearance gives way to a non-homogeneous condition brought about by the formation of holes or vacuoles in the interior and a fibrillar or lace-like net in the outer portions and in the processes. This phase is evidently one of intense activity, for cells which have undergone this loosening-up process change shape and position rapidly and are seen to undergo frequent mitoses.

The vacuoles enlarge and coalesce, and with the increase in the cavity thus formed is produced an anastomosing network of capillaries. Circulation of blood starts at about sixty hours.

This differentiation, occurring over a period of fourteen to fifteen hours, is not a steady progressive one in all cells. While the loosen-

[1] Am. Jour. of Anat., **vol. 18**, 1915.

ing up affects all angioblast cells, many revert to the homogenous phase. During at least two days after circulation starts there is continued formation of new vessels in the interstices of the first plexus, by the vacuolization of angioblast cells.

Throughout the process of angioblast migration, vacuolization and the formation of capillaries the angioblast cells remained specific and gave no indication of giving rise to erythrocytes or leukocytes.

Effect of Abdominal Thermal Applications on the Intraperitoneal Temperature.—S. Brill (from the Laboratory of Research Surgery and the Department of Surgery, Division B, University of Pennsylvania). Thermal applications have been used extensively as therapeutic agents. Although there is no doubt as to their efficacy in the treatment of a variety of clinical conditions, there is some question as to how they act when applied to the treatment of intraäbdominal lesions.

The effect of both heat and cold applications was studied on anesthetized and unanesthetized dogs, using the thermoelectric apparatus designed by Bazett and McGlone. Temperature readings were taken of the skin, subcutaneous tissue, deep tissue and peritoneal cavity. It was found that: (*a*) Cold applications had little effect on the intraperitoneal temperature, the greatest fall being 2.5° C., which was observed in one instance; (*b*) hot applications in the form of a hot-water bottle over a towel, as usually used clinically, did not produce any appreciable changes; (*c*) an electric pad did not influence the intraperitoneal temperature of the normal animal to any great extent, but in an animal under anesthesia with a low rectal temperature it caused a rise of 3.5° C. intraperitoneally. Coincidentally, the rectal temperature rose 2.4° C.

These observations indicate that the beneficial effects of hot and cold abdominal applications are due to other causes than the effect on intraperitonal temperature.

Bile Peritonitis and Bilous Ascites.—I. S. Ravdin and M. E. Morrison (from the Laboratory of Research Surgery, University of Pennsylvania). It is a well-established fact that the entrance of bile into the peritoneal cavity from a perforation in the extrahepatic biliary system will result in peritonitis if sufficient bile escapes. It is equally well established that the patient or animal may go for weeks or even months with large amounts of bile-stained fluid in the free peritoneal cavity without deleterious symptoms referable to the fluid itself. The clinician has frequently drawn no distinction between bile as such in the peritoneal cavity and the bile-stained fluid often found when portal stagnation and ductal obstruction are present. Contrary to the view of many surgeons, the authors have confirmed previous investigations that non-infected bile will cause bile peritonitis.

It was found that the bile-salt content of bilous ascitic fluid was extremely low when compared with the bile-salt content of fistula or gall-bladder bile. In the cases having innocuous bile-stained fluid in the peritoneal cavity in association with obstruction of the common duct, it is likely that this is the result of portal stagnation and transudation from the portal system. The low bile-salt content of the ascitic fluid can be explained by the observations of other investigators who

have found that after complete hepatic secretory suppression the bile-salt content of the blood returns to normal or subnormal values.

After concentration of the bilous ascitic fluid to a point where the bile salts were present in lethal doses, intraperitoneal injections killed mice in approximately the same period of time as equal concentrations of pure bile salts or of bile salts in gall-bladder or fistula bile. In a dog weighing 11 kilos, from which 150 cc. of bile-stained fluid was removed from the peritoneal cavity, the total bile-salt content was 0.255 gm. The amount of bile salts necessary to kill the animal within twenty-four hours would have been approximately 6.05 gm. (the amount of bile salts in 55 cc. of whole gall-bladder bile). The large amount of bile salts found in bile escaping from the extrahepatic ductal system will explain bile peritonitis, while the very low concentration found in the bilous ascitic fluid makes these accumulations apparently innocuous.

Anesthesia and Cell Division in Sea-urchin Eggs.—R. BLUMENTHAL (from the Zoölogical Laboratory, University of Pennsylvania). One of the chief criteria of anesthesia has been the reversible inhibition of cell division. The present experiments, however, show that anesthetics do not always prevent cell division. Fertilized arbacia eggs exposed to sea-water solutions of KCN, methyl, i-amyl, n-propyl and i-propyl alcohols in anesthetic concentrations will undergo cell division if the eggs are placed in these solutions within the ten minutes preceding the time when cell division is due. If the eggs cleave once and are permitted to remain in the anesthetics no further cleavage takes place.

It is suggested that cyanids act by preventing oxygen-protoplasm unions within the cell, although they do not prevent the utilization of the oxygen already in combination in the cell. As soon as this latter oxygen is used up, and since no further oxygen becomes available, development within the cell ceases.

Correction: On page 358 (March, 1929), under Chart III of Dr. Margolis' article on Chronic Pentosuria and Migraine the statement which reads "10.3 per cent pentose for February 21" should read "0.3 per cent pentose for February 21."

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